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VAR G4=30/CH2/33/36
VAR G5=OH/AK/17
VAR G6=AK/17
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 35

STEREO ATTRIBUTES: NONE
L5 1024 SEA FILE=REGISTRY SUB=L3 SSS FUL L4

100.0% PROCESSED 1028 ITERATIONS 1024 ANSWERS
SEARCH TIME: 00.00.01

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	198.79	1021.43

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-42.00

FILE 'MEDLINE' ENTERED AT 10:54:20 ON 28 SEP 2004

FILE 'HCAPLUS' ENTERED AT 10:54:20 ON 28 SEP 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE 'BIOSIS' ENTERED AT 10:54:20 ON 28 SEP 2004

FILE 'EMBASE' ENTERED AT 10:54:20 ON 28 SEP 2004

L6 9 FILE MEDLINE
L7 1034 FILE HCAPLUS
L8 5 FILE BIOSIS
L9 0 FILE EMBASE

TOTAL FOR ALL FILES
L10 1048 L5

=> s l10 and (postlesion? or post lesion? or neurodegenerat? or neurolog? degen? or alzheimer? or dement? or cognitive impairment or neural trauma)
L11 1 FILE MEDLINE
L12 12 FILE HCAPLUS
L13 0 FILE BIOSIS
L14 0 FILE EMBASE

TOTAL FOR ALL FILES
L15 13 L10 AND (POSTLESION? OR POST LESION? OR NEURODEGENERAT? OR NEURO LOG? DEGEN? OR ALZHEIMER? OR DEMENT? OR COGNITIVE IMPAIRMENT OR

Searched by: Mary Hale 571-272-2507 REM 1D86

Garcia
10/635797

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=> d l5 que stat;fil medl,hcapl,biosis,embase;s l5
L1              STR
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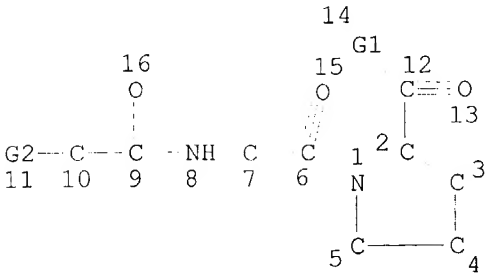


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 O  Ak
@17 18

NH Ak
19 @20

Ak  N  Ak
21 @22 23

 NH Ak
@27 28
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VAR G1=OH/17/NH2/20/22
VAR G2=NH2/22/27
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE
L3 1028 SEA FILE=REGISTRY SSS FUL L1
L4 STR

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@17 18      19 @20     21 @22 23     @27 28     @30 31
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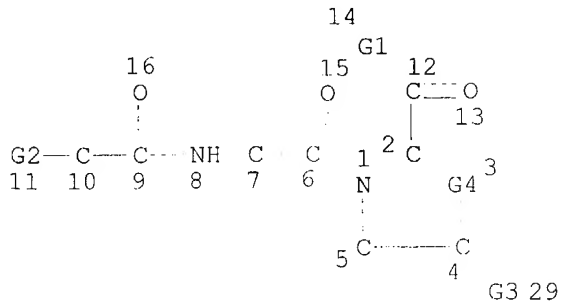


VAR G1=OH/17/NH2/20/22

Searched by: Mary Hale 571-272-2507 REM 1D86

NEURAL TRAUMA)

=> dup rem l15
PROCESSING COMPLETED FOR L15
L16 12 DUP REM L15 (1 DUPLICATE REMOVED)

=> d 1-12 cbib abs hitstr

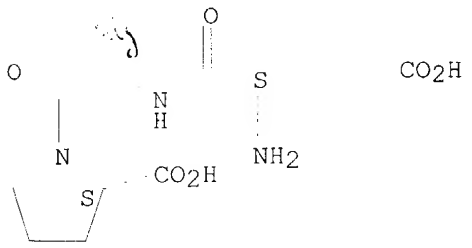
L16 ANSWER 1 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
2002:754121 Document No. 137:257696 Tripeptide GPE and analogs for regulation of weight. Alexi, Tajrena (Neuronz Limited, N. Z.). PCT Int. Appl. WO 2002076208 A1 20021003, 18 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US7686 20020315. PRIORITY: US 2001-PV278562 20010323.

AB Weight gain in a mammal, especially a human, having a condition that leads to decreased weight or weight loss, e.g. AIDS, brain trauma, a chronic **neurodegenerative** disease such as **Alzheimer**'s disease, Parkinson's disease, Huntington's disease, or multiple sclerosis, or other condition, is promoted by increasing the effective concentration of a GPE-related compound (GPE or a GPE analog) in the central nervous system of the mammal. This increase may be achieved by administration to the mammal of an effective amount of a GPE-related compound, a prodrug thereof, or an implant containing cells that express the GPE-related compound or prodrug.

IT **251471-78-0 401569-94-6**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tripeptide GPE and analogs for regulation of weight)

RN 251471-78-0 HCAPLUS
CN L-Proline, L-α-glutamylglycyl- (9CI) (CA INDEX NAME)

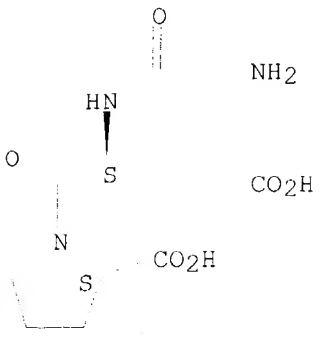
Absolute stereochemistry.



RN 401569-94-6 HCAPLUS
CN L-Proline, glycyl-L-α-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Searched by: Mary Hale 571-272-2507 REM 1D86



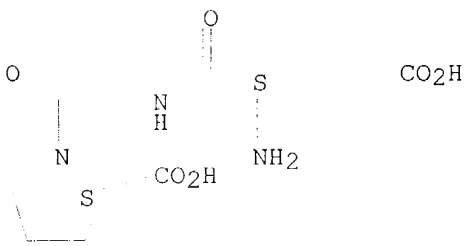
L16 ANSWER 2 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
2002:157813 Document No. 136:194268 GPE analogs. Gluckman, Peter; Alexi, Tajrena (Neuronz Limited, N. Z.). PCT Int. Appl. WO 2002016408 A2 20020228, 33 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US41883 20010824. PRIORITY: NZ 2000-506534 20000824.

AB The invention relates to GPE analogs, particularly GPE analogs capable of inducing an equivalent physiol. effect to GPE within a patient. Such GPE analogs include peptides where the Gly of Gly-Pro-Glu is replaced by any of Ala, Ser, Thr, or Pro; where the Pro of Gly-Pro-Glu is replaced by any of Ala, Ser, Thr, or Gly; and where the Glu of Gly-Pro-Glu is replaced by any of Asn, Asp, or Gln. The GPE analogs of the invention have application in any method of therapy or prophylaxis in which GPE has application. These applications include the treatment of acute brain injury and **neurodegenerative** disease, including but not limited to injury or disease in the CNS. The GPE analogs will normally be administered as part of a pharmaceutical composition or preparation

IT **251471-78-0 401569-94-6**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(GPE analogs and their use as neuroprotectants in relation to good permeability across blood-brain barrier)

RN 251471-78-0 HCAPLUS
CN L-Proline, L-α-glutamylglycyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

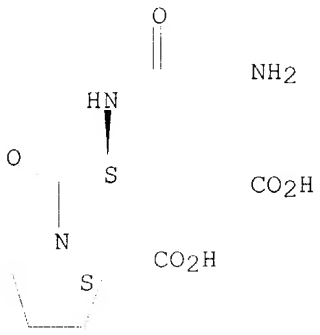


RN 401569-94-6 HCAPLUS

Searched by: Mary Hale 571-272-2507 REM 1D86

CN L-Proline, glycyl-L-α-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L16 ANSWER 3 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
2002:609523 Document No. 137:155181 Synthesis of tripeptides and tripeptide derivatives for the treatment of **neurodegenerative** diseases.
Rapin, Jean; Witzmann, Hans Klaus; Grumel, Jean-Marie; Gonella, Jacques (Tell-Pharm Ag, Switz.). Ger. Offen. DE 10105041 A1 20020814, 12 pp. (German). CODEN: GWXXBX. APPLICATION: DE 2001-10105041 20010205.

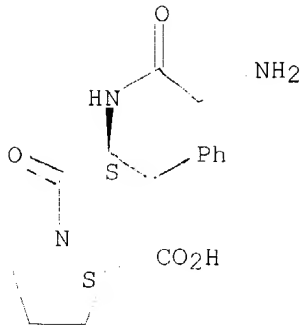
AB The invention concerns the use of tripeptide derivs. [e.g., H-Gly-Phe-Pro-NH2 (I)] for the treatment of **neurodegenerative** disease, such as **Alzheimer**'s disease. Thus, Boc-Phe-OH [Boc = (CH3)3OC(O)] was coupled with TFA.H-Pro-NH2 to give a dipeptide, which was N-deprotected and converted to its TFA salt for coupling with Boc-Gly-OH; the resulting protected tripeptide was N-deprotected and converted to its HCl salt. The blood-brain partition coeffs. of I and seventeen similar tripeptides were given. The plasma half-life of 14C-labeled I.HCl was determined in rats (no data). Using a rat model of **Alzheimer**'s disease, results of treatment with I showed retention of learned behavior in a five-day test of pole-climbing at a signal to avoid shock. Examination of subject brains revealed increase dendrite development in the hippocampus.

IT **52027-85-7 444884-54-2 444884-55-3**
444884-56-4 444884-57-5 444884-59-7
444884-64-4 444884-65-5 444884-66-6
444884-67-7 444884-68-8 444884-69-9
444884-70-2 444884-71-3
RL: PAC (Pharmacological activity); BIOL (Biological study)
(blood-brain partition coeffs. of as possible tripeptide agents for treatment of **neurodegenerative** disease)

RN 52027-85-7 HCAPLUS
CN L-Proline, glycyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

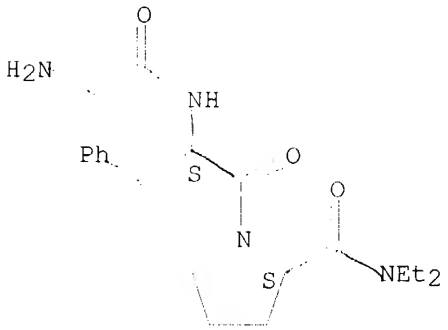
Absolute stereochemistry.

Searched by: Mary Hale 571-272-2507 REM 1D86



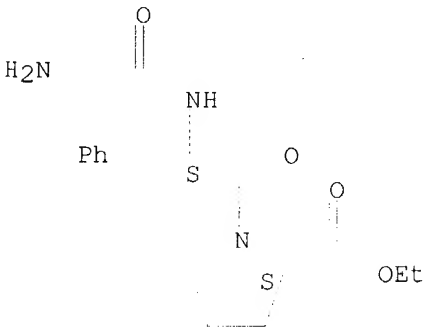
RN 444884-54-2 HCAPLUS
CN L-Prolinamide, glycyl-L-phenylalanyl-N,N-diethyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 444884-55-3 HCAPLUS
CN L-Proline, glycyl-L-phenylalanyl-, ethyl ester (9CI) (CA INDEX NAME)

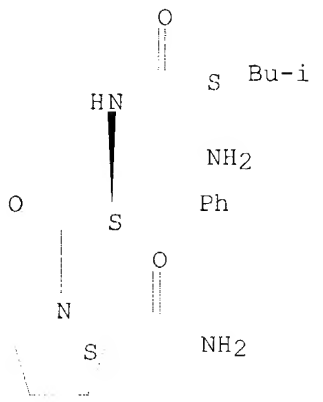
Absolute stereochemistry.



RN 444884-56-4 HCAPLUS
CN L-Prolinamide, L-leucyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

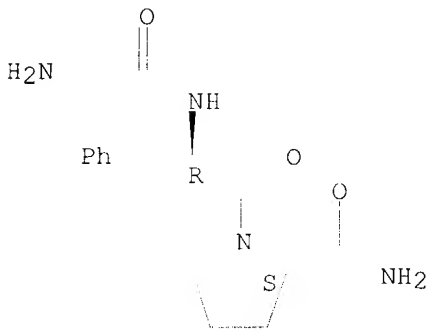
Absolute stereochemistry.

Searched by: Mary Hale 571-272-2507 REM 1D86



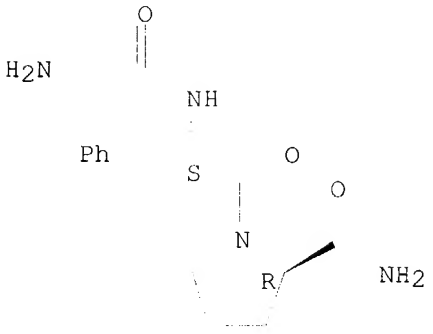
RN 444884-57-5 HCAPLUS
CN L-Prolinamide, glycyl-D-phenylalanyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 444884-59-7 HCAPLUS
CN D-Prolinamide, glycyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

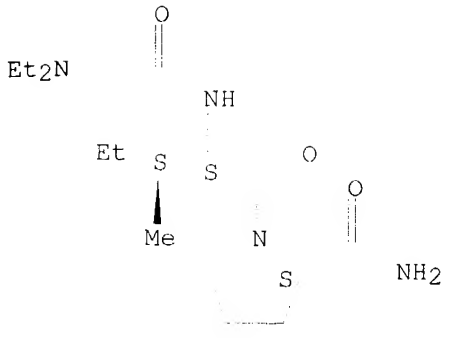
Absolute stereochemistry.



RN 444884-64-4 HCAPLUS
CN L-Prolinamide, N,N-diethylglycyl-L-isoleucyl- (9CI) (CA INDEX NAME)

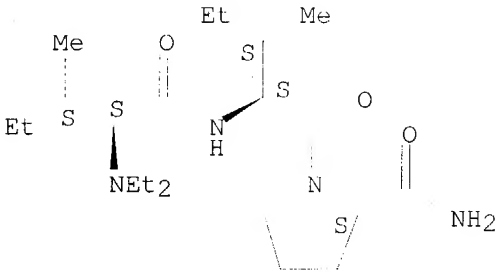
Absolute stereochemistry.

Searched by: Mary Hale 571-272-2507 REM 1D86



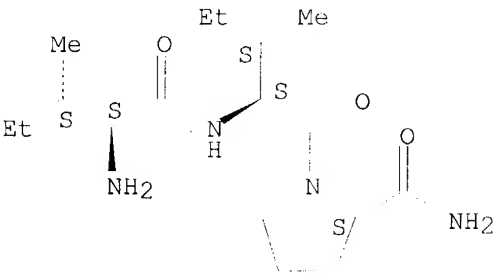
RN 444884-65-5 HCAPLUS
CN L-Prolinamide, N,N-diethyl-L-isoleucyl-L-isoleucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 444884-66-6 HCAPLUS
CN L-Prolinamide, L-isoleucyl-L-isoleucyl- (9CI) (CA INDEX NAME)

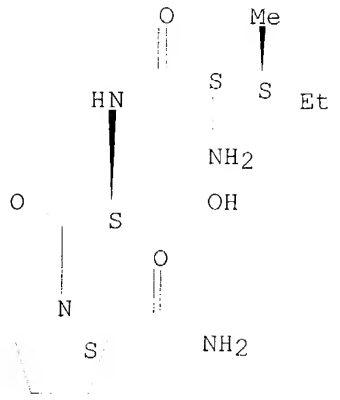
Absolute stereochemistry.



RN 444884-67-7 HCAPLUS
CN L-Prolinamide, L-isoleucyl-L-seryl- (9CI) (CA INDEX NAME)

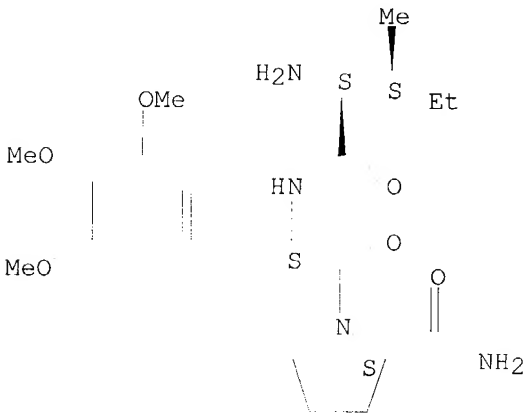
Absolute stereochemistry.

Searched by: Mary Hale 571-272-2507 REM 1D86



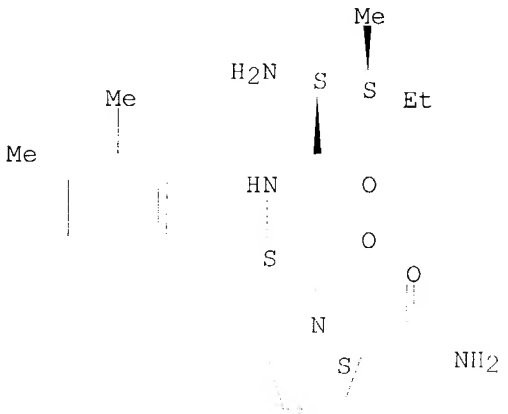
RN 444884-68-8 HCAPLUS
CN L-Prolinamide, L-isoleucyl-3,5-dimethoxy-O-methyl-L-tyrosyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 444884-69-9 HCAPLUS
CN L-Prolinamide, L-isoleucyl-3,4-dimethyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

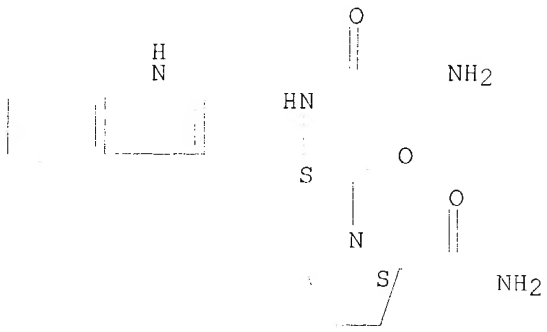
Absolute stereochemistry.



Searched by: Mary Hale 571-272-2507 REM 1D86

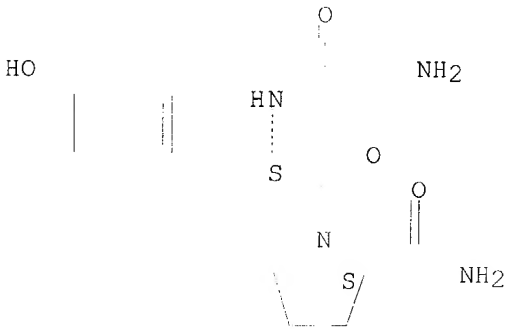
RN 444884-70-2 HCAPLUS
CN L-Prolinamide, glycyl-L-tryptophyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



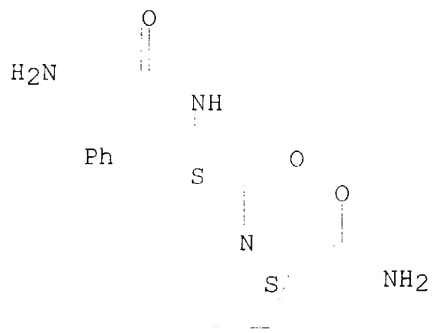
RN 444884-71-3 HCAPLUS
CN L-Prolinamide, glycyl-L-tyrosyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **109776-77-4P 444884-53-1P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of for the treatment of **neurodegenerative** disease)
RN 109776-77-4 HCAPLUS
CN L-Prolinamide, glycyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

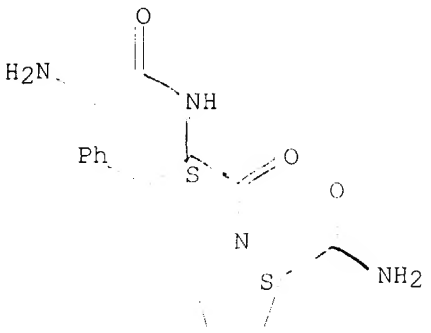
Absolute stereochemistry. Rotation (-).



Searched by: Mary Hale 571-272-2507 REM 1D86

RN 444884-53-1 HCAPLUS
CN L-Prolinamide, glycyl-L-phenylalanyl-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



● HCl

L16 ANSWER 4 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
2002:609521 Document No. 137:140781 Synthesis of tripeptides and tripeptide derivatives for the treatment of **post lesional** diseases of the nervous system.. Rapin, Jean; Witzmann, Hans Klaus; Grumel, Jean-Marie; Gonella, Jacques (Tell-Pharm Ag, Switz.). Ger. Offen. DE 10105038 A1 20020814, 10 pp. (German). CODEN: GWXXBX. APPLICATION: DE 2001-10105038 20010205.

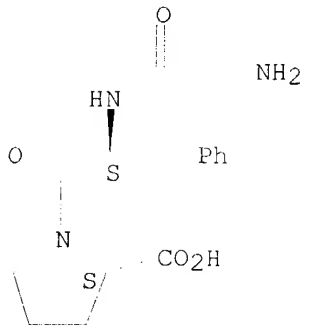
AB The invention concerns the use of tripeptide derivs. [e.g., H-Gly-Phe-Pro-NH2 (I)] for the treatment of **post lesional** diseases of the nervous system. Thus, Boc-Phe-OH [Boc = (CH3)3OC(O)] was coupled with TFA.H-Pro-NH2 to give a dipeptide, which was N-deprotected and converted to its TFA salt for coupling with Boc-Gly-OH; the resulting protected tripeptide was N-deprotected and converted to its HCl salt. The blood-brain partition coeffs. of I and seventeen similar tripeptides were given. The plasma half-life of 14C-labeled I.HCl was determined in rats (no data). Using an in-vivo dendritic sprouting assay in rats, I was tested for effect on hippocampus septum, and showed growth of up to 2μm, compared to controls.

IT **52027-85-7 444884-54-2 444884-55-3**
444884-56-4 444884-57-5 444884-59-7
444884-64-4 444884-65-5 444884-66-6
444884-67-7 444884-68-8 444884-69-9
444884-70-2 444884-71-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(blood-brain partition coeffs. of as possible tripeptide agents for treatment of lesional nerve disease)

RN 52027-85-7 HCAPLUS
CN L-Proline, glycyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

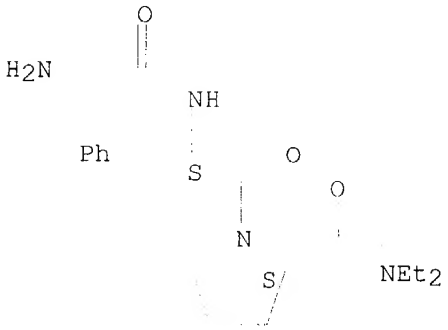
Absolute stereochemistry.

Searched by: Mary Hale 571-272-2507 REM 1D86



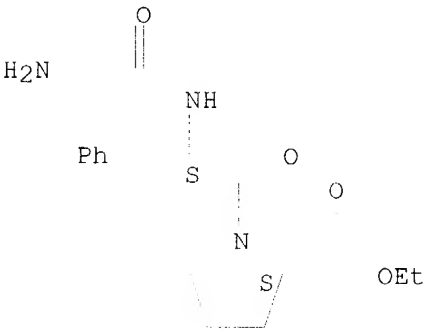
RN 444884-54-2 HCAPLUS
CN L-Prolinamide, glycyl-L-phenylalanyl-N,N-diethyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 444884-55-3 HCAPLUS
CN L-Proline, glycyl-L-phenylalanyl-, ethyl ester (9CI) (CA INDEX NAME)

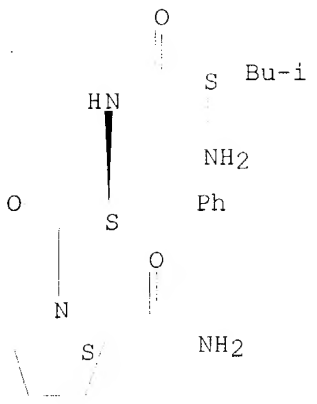
Absolute stereochemistry.



RN 444884-56-4 HCAPLUS
CN L-Prolinamide, L-leucyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

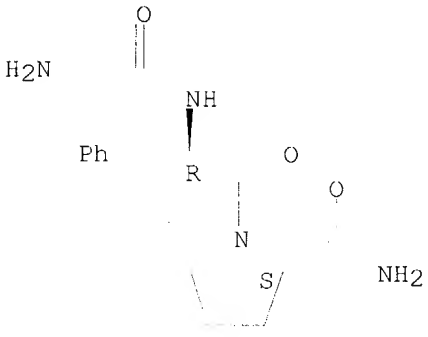
Absolute stereochemistry.

Searched by: Mary Hale 571-272-2507 REM 1D86



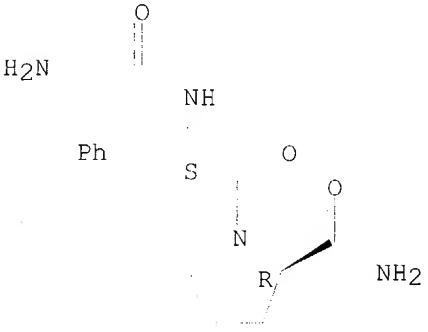
RN 444884-57-5 HCAPLUS
CN L-Prolinamide, glycyl-D-phenylalanyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 444884-59-7 HCAPLUS
CN D-Prolinamide, glycyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

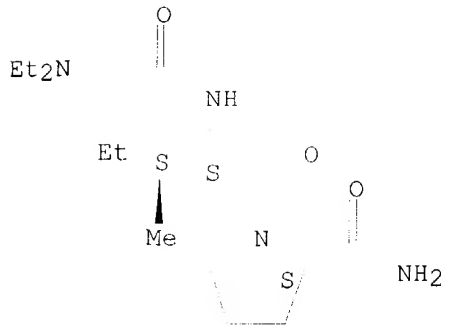
Absolute stereochemistry.



RN 444884-64-4 HCAPLUS
CN L-Prolinamide, N,N-diethylglycyl-L-isoleucyl- (9CI) (CA INDEX NAME)

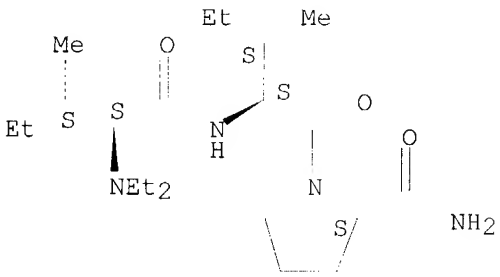
Absolute stereochemistry.

Searched by: Mary Hale 571-272-2507 REM 1D86



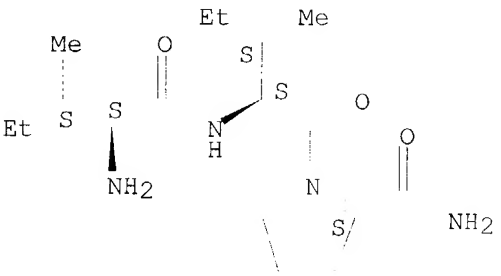
RN 444884-65-5 HCAPLUS
CN L-Prolinamide, N,N-diethyl-L-isoleucyl-L-isoleucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 444884-66-6 HCAPLUS
CN L-Prolinamide, L-isoleucyl-L-isoleucyl- (9CI) (CA INDEX NAME)

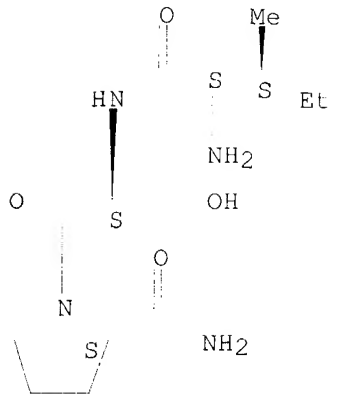
Absolute stereochemistry.



RN 444884-67-7 HCAPLUS
CN L-Prolinamide, L-isoleucyl-L-seryl- (9CI) (CA INDEX NAME)

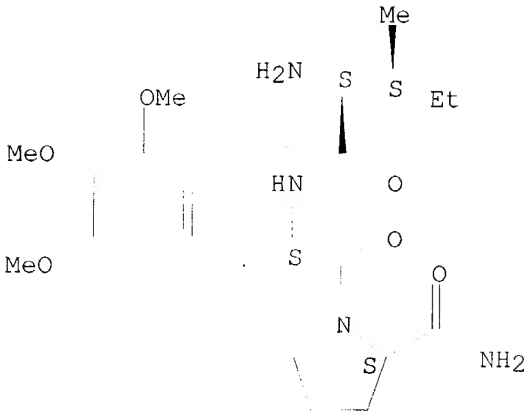
Absolute stereochemistry.

Searched by: Mary Hale 571-272-2507 REM 1D86



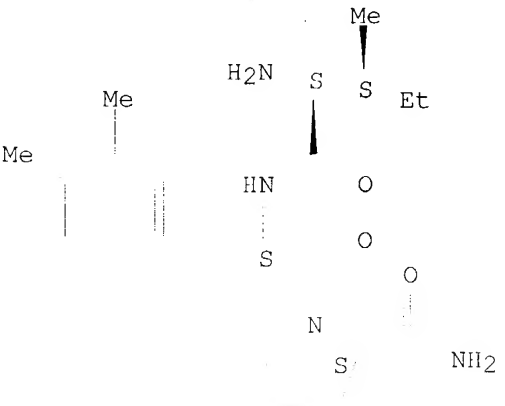
RN 444884-68-8 HCAPLUS
CN L-Prolinamide, L-isoleucyl-3,5-dimethoxy-O-methyl-L-tyrosyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 444884-69-9 HCAPLUS
CN L-Prolinamide, L-isoleucyl-3,4-dimethyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

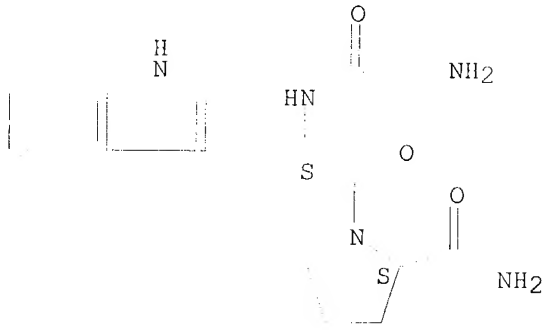
Absolute stereochemistry.



Searched by: Mary Hale 571-272-2507 REM 1D86

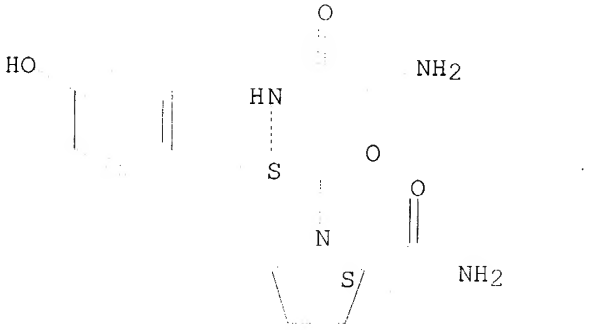
RN 444884-70-2 HCAPLUS
CN L-Prolinamide, glycyl-L-tryptophyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



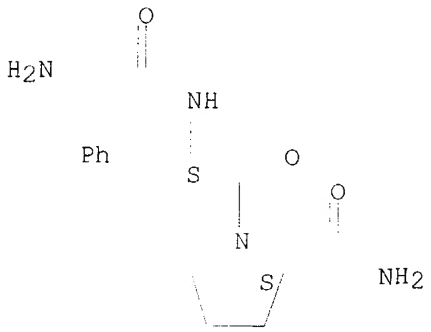
RN 444884-71-3 HCAPLUS
CN L-Prolinamide, glycyl-L-tyrosyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **109776-77-4P 444884-53-1P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of for treatment of lesional nerve disease)
RN 109776-77-4 HCAPLUS
CN L-Prolinamide, glycyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

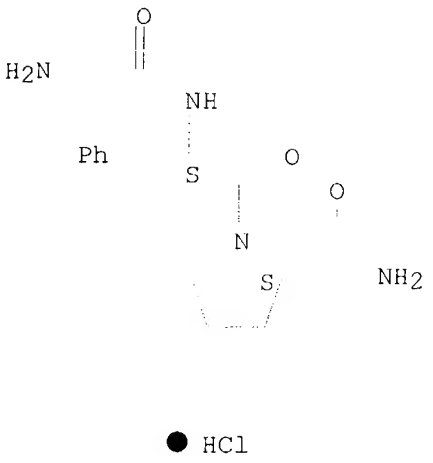
Absolute stereochemistry. Rotation (-).



Searched by: Mary Hale 571-272-2507 REM 1D86

RN 444884-53-1 HCAPLUS
CN L-Prolinamide, glycyl-L-phenylalanyl-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



● HCl

L16 ANSWER 5 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
2001:582172 Document No. 135:151170 Analytical method to evaluate animal models of neurofibrillary degeneration. Roder, Hanno (Nap A.-G., Germany). PCT Int. Appl. WO 2001057535 A2 20010809, 30 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-EP1053 20010201. PRIORITY: EP 2000-102057 20000202.

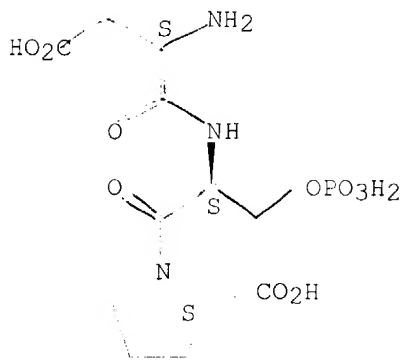
AB The present invention relates to methods for modeling aspects of **Alzheimer**'s disease (AD), in particular the present invention relates to methods for modeling abnormal tau hyperphosphorylation as the key step to the process of neurofibrillary degeneration and tau aggregation. In one model, rats were intracerebrally injected with okadaic acid to induce neurofibrillary changes.

IT **353246-01-2**
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(abnormal tau hyperphosphorylation induction to mimic neurofibrillary degeneration and tau aggregation in **Alzheimer**'s disease model)

RN 353246-01-2 HCAPLUS
CN L-Proline, L-α-aspartyl-O-phosphono-L-seryl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Searched by: Mary Hale 571-272-2507 REM 1D86



L16 ANSWER 6 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
2001:167773 Document No. 134:204745 Peptides and substances, methods and devices using same for diagnosing and treating **neurodegenerative** disorders. Michaelson, Daniel M. (Ramot University Authority for Applied Research & Industrial Development, Israel). PCT Int. Appl. WO 2001015655 A2 20010308, 117 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-IL509 20000827. PRIORITY: US 1999-386347 19990831; US 2000-PV221150 20000727.

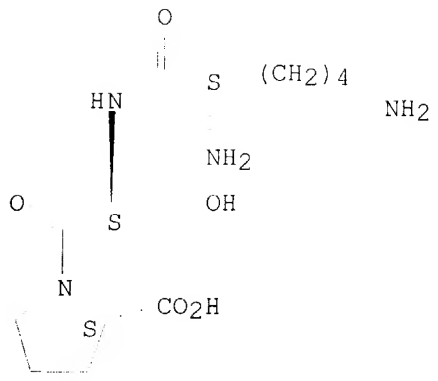
AB A method of identifying an existence, non-existence, type or state of a **neurodegenerative** disorder in an individual. The method is effected by (a) immunoreacting with a serum sample derived from the individual at least one peptide representing at least one epitope derived from an endogenous protein to which at least one antibody is produced in vivo at onset or during progression of the **neurodegenerative** disorder, the at least one peptide being selected such that the at least one antibody being capable of immunobinding with the at least one peptide; and (b) detecting a presence, absence or degree of the immunobinding to thereby identify the existence, non-existence, type or state of the **neurodegenerative** disorder.

IT **142861-12-9**
RL: ARG (Analytical reagent use); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(peptides and devices for diagnosing and treating **neurodegenerative** disorders)

RN 142861-12-9 HCAPLUS
CN L-Proline, L-lysyl-L-seryl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Searched by: Mary Hale 571-272-2507 REM 1D86



L16 ANSWER 7 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
2001:31330 Document No. 134:95509 Method of reducing neuronal injury or apoptosis using a p38 mitogen-activated protein kinase inhibitor. Lipton, Stuart A. (USA). PCT Int. Appl. WO 2001001986 A1 20010111, 34 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US18385 20000630. PRIORITY: US 1999-PV142341 19990702.

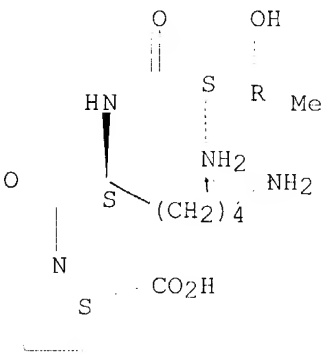
AB A method is provided for reducing neuronal injury or apoptosis including administering to a patient in need thereof an effective amount of a p38 mitogen-activated protein kinase (MAPK) inhibitor. Methods of treating an HIV-mediated **dementia**, glaucoma, or other **neurodegenerative** disorders are also disclosed.

IT **41961-56-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(p38 MAPK inhibitor for reducing neuronal injury or apoptosis)

RN 41961-56-2 HCAPLUS

CN L-Proline, L-threonyl-L-lysyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L16 ANSWER 8 OF 12 MEDLINE on STN DUPLICATE 1
1999324215. PubMed ID: 10393974. Chemokines and activated macrophages in

Searched by: Mary Hale 571-272-2507 REM 1D86

HIV gp120-induced neuronal apoptosis. Kaul M; Lipton S A. (CNS Research Institute, Brigham and Women's Hospital, and Program in Neuroscience, Harvard Medical School, Boston, MA 02115, USA.) Proceedings of the National Academy of Sciences of the United States of America, (1999 Jul 6) 96 (14) 8212-6. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB HIV-1 glycoprotein gp120 induces injury and apoptosis in rodent and human neurons in vitro and in vivo and is therefore thought to contribute to HIV-associated **dementia**. In addition to CD4, different gp120 isolates bind to the alpha- or beta-chemokine receptors CXCR4 and CCR5, respectively. These and other chemokine receptors are on brain macrophages/microglia, astrocytes, and neurons. Thus, apoptosis could occur via direct interaction of gp120 with neurons, indirectly via stimulation of glia to release neurotoxic factors, or via both pathways. Here we show in rat cerebrocortical cultures that recapitulate the type and proportion of cells normally found in brain, i.e., neurons, astrocytes, and macrophages/microglia, that the beta-chemokines RANTES (regulated on activation, normal T cell expressed and secreted) and macrophage inflammatory protein (MIP-1beta) protect neurons from gp120SF2-induced apoptosis. The gp120SF2 isolate prefers binding to CXCR4 receptors, similar to the physiological alpha-chemokine ligands, stromal cell-derived factor (SDF)-1alpha/beta. SDF-1alpha/beta failed to prevent gp120SF2 neurotoxicity, and in fact also induced neuronal apoptosis. We could completely abrogate gp120SF2-induced neuronal apoptosis with the tripeptide TKP, which inhibits activation of macrophages/microglia. In contrast, TKP or depletion of macrophages/microglia did not prevent SDF-1 neurotoxicity. Inhibition of p38 mitogen-activated protein kinase ameliorated both gp120SF2- and SDF-1-induced neuronal apoptosis. Taken together, these results suggest that gp120SF2 and SDF-1 differ in the cell type on which they stimulate CXCR4 to induce neuronal apoptosis, but both ligands use the p38 mitogen-activated protein kinase pathway for death signaling. Moreover, gp120SF2-induced neuronal apoptosis depends predominantly on an indirect pathway via activation of chemokine receptors on macrophages/microglia, whereas SDF-1 may act directly on neurons or astrocytes.

L16 ANSWER 9 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN

1998:175943 Document No. 128:226237 Anti-inflammatory peptides and therapeutic uses thereof. Eisenbach-Schwartz, Michal; Beserman, Pierre; Hirschberg, David L. (Yeda Research and Development Co. Ltd., Israel; Eisenbach-Schwartz, Michal; Beserman, Pierre; Hirschberg, David L.). PCT Int. Appl. WO 9809985 A2 19980312, 44 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-IL295 19970903. PRIORITY: US 1996-25376 19960903; US 1996-753141 19961120; US 1997-864301 19970528.

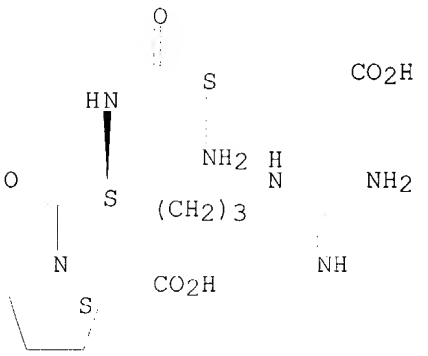
AB The invention is directed to peptides of the formulas (i) Xaa-Yaa-Arg (either Xaa is any amino acid residue and Yaa is Glu or Xaa is absent and Yaa is any amino acid residue with the exception of Pro), (ii) Arg-Yaa-Xaa (either Xaa is any amino acid residue and Yaa is Glu or Xaa is absent and Yaa is any amino acid residue with the exception of Asn), (iii) Xaa-Arg-Yaa (Xaa is any amino acid residue and Yaa is Glu), and (i.v.) Yaa-Arg-Xaa (Xaa is any amino acid residue and Yaa is Glu), and to derivs. thereof, which exert an inhibitory effect on macrophage migration and/or macrophage phagocytic activity. In addition, the peptides and derivs. thereof exert an inhibitory effect on the ability of macrophages and T cells to adhere to extracellular matrix and/or fibronectin. The peptides

and derivs. thereof exert an inhibitory effect on a humoral and/or cellular immune response. The invention is also directed to methods for use of the peptides and derivs. thereof and compns. containing them for the inhibition of inflammation, including but not limited to, inflammation at a joint, in the central nervous system generally, at specific lesions in the central nervous system, and other immune privileged sites. Immune privilege factor was purified from brain conditioned medium and shown to have a similar migration pattern to Glu-Arg.

IT **131837-03-1 175175-43-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-inflammatory peptides and therapeutic uses)

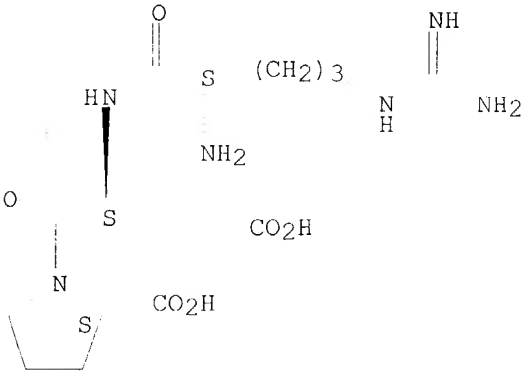
RN 131837-03-1 HCAPLUS
CN L-Proline, L-α-glutamyl-L-arginyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 175175-43-6 HCAPLUS
CN L-Proline, L-arginyl-L-α-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L16 ANSWER 10 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
1998:52717 Document No. 128:139388 Neurotoxic responses by microglia elicited by excitotoxic injury in the mouse hippocampus. Rogove, A. D.; Tsirka, S. E. (Univ. Med. Center Stony Brook, Stony Brook, NY, 11794-8651, USA). Current Biology, 8(1), 19-25 (English) 1998. CODEN: CUBLE2. ISSN: 0960-9822. Publisher: Current Biology Ltd..

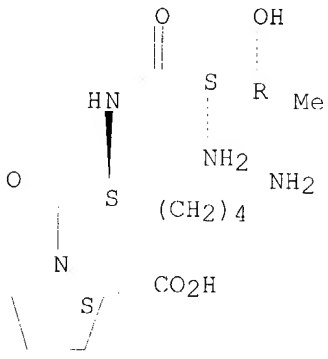
AB Injury to the brain induces dramatic local changes in gene expression, cellular morphol. and behavior. Activation of microglial cells occurs as

an early event after central nervous system (CNS) injury, but it has not been determined whether such activation plays a casual role in neuronal death. We have investigated this question using an excitotoxin-mediated brain injury model system, in conjunction with an endogenous peptide factor (macrophage/microglial inhibiting factor, MIF) that ablates microglial contribution to the cascade. Using MIF, we inhibited the microglial activation that normally follows excitotoxic injury. In cell culture studies, we found that such inhibition blocked the rapid release of microglia-derived tissue plasminogen activator (tPA), an extracellular serine protease made by both neurons and microglia, which we had previously identified as mediating a critical step in excitotoxin-induced neuronal death. Finally, infusion of MIF into the mouse brain prior to excitotoxic insult resulted in the protection of neurons from cell death. Our results demonstrate that microglia undertake a neurotoxic role when excitotoxic injury occurs in the CNS. The also suggest that the tPA released from microglia has a critical role in triggering **neurodegeneration.**

IT **41961-56-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(neurotoxic responses by microglia elicited by excitotoxic injury in mouse hippocampus)

RN 41961-56-2 HCAPLUS
CN L-Proline, L-threonyl-L-lysyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L16 ANSWER 11 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
1997:168787 Document No. 126:233774 Effect of active fragments of arginine-vasopressin on the disturbance of spatial cognition in rats.
Fujiwara, Michihiro; Ohgami, Yusuke; Inada, Kenichi; Iwasaki, Katsunori
(Dep. Physiology Pharmacology, Fukuoka univ., Fukuoka, 814-80, Japan).
Behavioural Brain Research, 83(1/2), 91-96 (English) 1997. CODEN: BBREDI.
ISSN: 0166-4328. Publisher: Elsevier.

AB The effect of arginine8-vasopressin (AVP1-9) and its metabolite C-terminal fragments on the scopolamine-induced disruption of spatial cognition were investigated using an 8-arm radial maze task in rats, AVP1-9 (10 μg/kg s.c.) markedly improved the disruption of spatial cognition by treatment with scopolamine (0.5 mg/kg i.p.), and 60% of the rats recovered to a normal level. The main metabolite of AVP1-9 (0.5 and 1 ng/kg s.c.) also significantly improved the scopolamine-induced deficit of spatial memory. The activity of AVP4-9 was determined to be abut 10,000 fold greater than that of AVP1-9. An intracerebroventricular (i.c.v.) injection of 10 fg of AVP5-8, however, showed a lower activity. Both AVP6-8 and AVP5-7, which are both metabolites of AVP5-8, demonstrated no activity. The scopolamine-induced disruption of spatial memory improved after

Searched by: Mary Hale 571-272-2507 REM 1D86

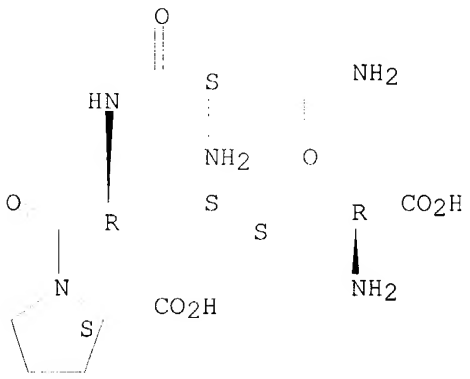
microinjection of AVP4-9 (10 fg) into the ventral hippocampus (VH) region, but not into the dorsal hippocampus. In an in vivo microdialysis study, the scopolamine-induced acetylcholine (ACh) release from the VH was slightly potentiated by treatment with AVP4-9 (10 fg i.c.v.). In addition, an AVP4-9 analog, which is a synthetic hexapeptide and has a longer half-life, also demonstrated a markedly improved effect, which had a 10-fold higher activity than that with AVP4-9. AVP4-9 is the most potent activity of all the endogenous metabolites of the AVP1-9 and the new synthetic AVP4-9 analog, that substitutes Ser for Cys-Cys in hexapeptide, has higher activity than that of AVP4-9. These results indicate that [Ser6] hexapeptide has an important role in behavioral activity. Based on these results, it is possible that AVP1-9 and its metabolite AVP4-9 could be useful in treating cholinergic dysfunction diseases, such as **Alzheimer**'s disease. Hexapeptide may play an important role in improving the spatial memory by promoting the release of ACh in the VH region.

IT **188477-77-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(vasopressin fragments effect on disturbance of spatial cognition in rats)

RN 188477-77-2 HCAPLUS

CN L-Proline, L-asparaginyl-L-cysteinyl-, disulfide with L-cysteine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L16 ANSWER 12 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN

1995:551053 Document No. 123:27227 Human TRH receptor, its production via DNA cloning, and its use for neuropathy treatment and agonist/antagonist screening. Hinuma, Shuji; Hosoya, Masaki; Ondo, Haruo (Japan). Eur. Pat. Appl. EP 638645 A1 19950215, 51 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE. (English). CODEN: EPXXDW. APPLICATION: EP 1994-112311 19940806. PRIORITY: JP 1993-UT19830 19930810; JP 1993-286986 19931116; JP 1993-325215 19931222; JP 1994-44497 19940316.

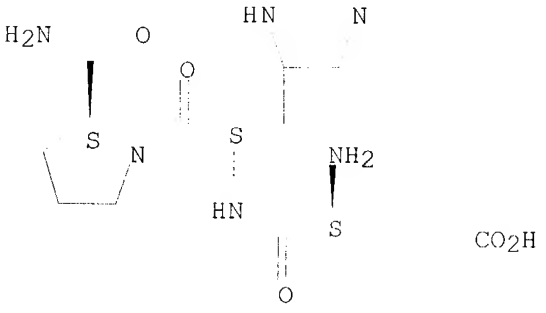
AB A human receptor protein capable of binding TRH, a DNA coding for said protein, use of the protein and DNA, a method for preparing said protein, and antibodies to the protein are described. The human TRH receptor protein and the DNA coding for the protein of the present invention are useful as (1) a diagnostic composition for neuropathy (particularly, **dementia**), (2) a pharmaceutical composition for neuropathy and (3) a material used for screening a TRH receptor agonist or antagonist. Thus, rat TRH receptor cDNA was used to screen a human genomic DNA library and isolate fragments containing exon and exon 2, which together coded for the 398 amino acids of the human receptor protein. Standard genetic techniques were used to ligate

the coding regions of the 2 fragments into a single full-length coding DNA, and for subsequent expression of human TRH receptor using baculovirus in Sf9 cells or CHO dhfr- cells. Human TRH receptor agonist or antagonists compds. could be screened in the CHO cells by their ability to antagonize the binding of TRH, affect the release of arachidonic acid, or by using a secretive alkaline phosphatase gene linked to a c-fos promoter in a TRH receptor expression cell. Nineteen TRH analogs were tested for TRH binding antagonistic activity. Partial human TRH receptor peptides deduced to be extracellular region (hydrophilic sites) in hydrophobic plot anal. also have TRH receptor activity and can be used the the same purposes and the whole protein.

IT **51826-17-6**
RL: ANT (Analyte); ANST (Analytical study)
(human TRH receptor, its production via DNA cloning, and its use for neuropathy treatment and agonist/antagonist screening)

RN 51826-17-6 HCAPLUS
CN L-Prolinamide, L-α-glutamyl-L-histidyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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=> s l10 and (mental disorder(1)cognitive or cognition(1)disorder)
L17           0 FILE MEDLINE
L18           1 FILE HCAPLUS
L19           0 FILE BIOSIS
L20           0 FILE EMBASE

TOTAL FOR ALL FILES
L21           1 L10 AND (MENTAL DISORDER(L) COGNITIVE OR COGNITION(L) DISORDER)

=> d cbib abs hitstr

L21  ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2004 ACS on STN
2001:167773  Document No. 134:204745  Peptides and substances, methods and
     devices using same for diagnosing and treating neurodegenerative
     disorders. Michaelson, Daniel M. (Ramot University Authority for Applied
     Research & Industrial Development, Israel). PCT Int. Appl. WO 2001015655
     A2 20010308, 117 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ,
     BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES,
     FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ,
     LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL,
     PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,
     VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ,
     CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC,
     ML, MR, NE, NL, PT, SE, SN, TD, TG.  (English).  CODEN: PIXXD2.
     APPLICATION: WO 2000-IL509 20000827.  PRIORITY: US 1999-386347 19990831;
     US 2000-PV221150 20000727.
```

Searched by: Mary Hale 571-272-2507 REM 1D86

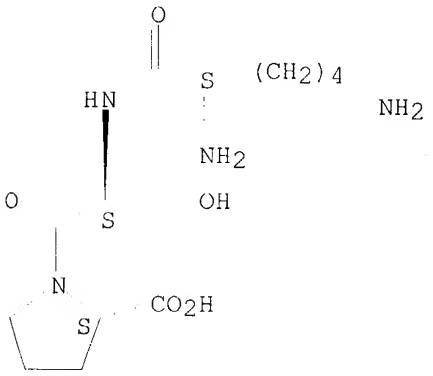
AB A method of identifying an existence, non-existence, type or state of a neurodegenerative disorder in an individual. The method is effected by (a) immunoreacting with a serum sample derived from the individual at least one peptide representing at least one epitope derived from an endogenous protein to which at least one antibody is produced in vivo at onset or during progression of the neurodegenerative disorder, the at least one peptide being selected such that the at least one antibody being capable of immunobinding with the at least one peptide; and (b) detecting a presence, absence or degree of the immunobinding to thereby identify the existence, non-existence, type or state of the neurodegenerative disorder.

IT **142861-12-9**
RL: ARG (Analytical reagent use); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(peptides and devices for diagnosing and treating neurodegenerative disorders)

RN 142861-12-9 HCAPLUS

CN L-Proline, L-lysyl-L-seryl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> fil reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	123.59	1145.02

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-8.40	-50.40

FILE 'REGISTRY' ENTERED AT 10:56:06 ON 28 SEP 2004

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 27 SEP 2004 HIGHEST RN 752974-11-1
DICTIONARY FILE UPDATES: 27 SEP 2004 HIGHEST RN 752974-11-1

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Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

```
=> s "glycyl-l-phenylalanyl-l-prolineamide"/cn
L22           0 "GLYCYL-L-PHENYLALANYL-L-PROLINEAMIDE"/CN

=> e "glycyl-l-phenylalanyl-l-prolineamide"/cn
E1            1      GLYCYL-L-PHENYLALANYL-L-PHENYLALANINE HEMIHYDRATE/CN
E2            1      GLYCYL-L-PHENYLALANYL-L-PHENYLALANYL-L-TYROSYL-L-THREONYL-L-
                     PROLYL-(E-PHENYLTHIOCARBAMOYL)-L-LYSYL-L-ALANINE/CN
E3            0 --> GLYCYL-L-PHENYLALANYL-L-PROLINEAMIDE/CN
E4            1      GLYCYL-L-PHENYLALANYLGLYCINE/CN
E5            1      GLYCYL-L-PROLINE/CN
E6            1      GLYCYL-L-PROLINE B-NAPHTHYLAMIDE/CN
E7            1      GLYCYL-L-PROLINE DIPEPTIDASE/CN
E8            1      GLYCYL-L-PROLINE HOMOPOLYMER/CN
E9            1      GLYCYL-L-PROLINE HYDROLASE/CN
E10           1      GLYCYL-L-PROLINE LACTAM/CN
E11           1      GLYCYL-L-PROLINE P-(PHENYLAZO)ANILIDE TOSYLATE/CN
E12           1      GLYCYL-L-PROLINE-1-NAPHTHYLAMIDE HYDROCHLORIDE/CN

=> e "n,n-diethyl-isoleucyl-phenylalanyl-l-proline ethylamide"/cn
E1            1      N,N-DIETHYL-DL-ALANINE/CN
E2            1      N,N-DIETHYL-DL-MANDELAMIDE/CN
E3            0 --> N,N-DIETHYL-ISOLEUCYL-PHENYLALANYL-L-PROLINE ETHYLAMIDE/CN
E4            1      N,N-DIETHYL-L-ALANINE/CN
E5            1      N,N-DIETHYL-L-ALANINE METHYL ESTER/CN
E6            1      N,N-DIETHYL-L-PHENOXYPROPIONAMIDE/CN
E7            1      N,N-DIETHYL-M-AMINOACETANILIDE/CN
E8            1      N,N-DIETHYL-M-AMINOPHENOL/CN
E9            1      N,N-DIETHYL-M-ANISIDINE/CN
E10           1      N,N-DIETHYL-M-CHLOROANILINE/CN
E11           1      N,N-DIETHYL-M-ETHYLANILINE/CN
E12           1      N,N-DIETHYL-M-FLUOROBENZAMIDE/CN

=> e "n,n-diethyl-isoleucyl-isoleucyl-prolineamide"/cn
E1            1      N,N-DIETHYL-DL-ALANINE/CN
E2            1      N,N-DIETHYL-DL-MANDELAMIDE/CN
E3            0 --> N,N-DIETHYL-ISOLEUCYL-ISOLEUCYL-PROLINEAMIDE/CN
E4            1      N,N-DIETHYL-L-ALANINE/CN
E5            1      N,N-DIETHYL-L-ALANINE METHYL ESTER/CN
E6            1      N,N-DIETHYL-L-PHENOXYPROPIONAMIDE/CN
E7            1      N,N-DIETHYL-M-AMINOACETANILIDE/CN
E8            1      N,N-DIETHYL-M-AMINOPHENOL/CN
E9            1      N,N-DIETHYL-M-ANISIDINE/CN
E10           1      N,N-DIETHYL-M-CHLOROANILINE/CN
E11           1      N,N-DIETHYL-M-ETHYLANILINE/CN
E12           1      N,N-DIETHYL-M-FLUOROBENZAMIDE/CN

=> fil medl,hcapl,embase,biosis,wpids
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                5.69    1150.71

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)    SINCE FILE      TOTAL
                                                   ENTRY    SESSION
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=> s diethyl(l)isoleucyl(l)isoleucyl(l)prolineamide
L23 0 FILE MEDLINE
L24 0 FILE HCAPLUS
L25 0 FILE EMBASE
L26 0 FILE BIOSIS
L27 0 FILE WPIDS

TOTAL FOR ALL FILES
L28 0 DIETHYL(L) ISOLEUCYL(L) ISOLEUCYL(L) PROLINEAMIDE

=> s diethyl(l)isoleucyl(l)phenylalanyl(l)proline(l)ethylamide
L29 0 FILE MEDLINE
L30 0 FILE HCAPLUS
L31 0 FILE EMBASE
L32 0 FILE BIOSIS
L33 0 FILE WPIDS

TOTAL FOR ALL FILES
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=> s glycyl(l)phenylalanyl(l)prolineamide
L35 0 FILE MEDLINE
L36 0 FILE HCAPLUS
L37 0 FILE EMBASE
L38 1 FILE BIOSIS
L39 0 FILE WPIDS

TOTAL FOR ALL FILES
L40 1 GLYCYL(L) PHENYLALANYL(L) PROLINEAMIDE

=> d cbib abs

L40 ANSWER 1 OF 1 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
1987:68760 Document No.: PREV198783037086; BA83:37086. SYNTHESIS OF A POTENT ENKEPHALIN ANALOG TYROSYL-D-THREONYL-**GLYCYL-PHENYLALANYL**-DEHYDRO **PROLINEAMIDE** AND SOME OF ITS BIOLOGICAL ACTIVITIES.
TZOUGRAKI C [Reprint author]; DAIRMAN W M; MAKOFSKE R C; AEPPLI L; MEIENHOFER J. LAB ORGANIC CHEM, UNIV ATHENS, ATHENS 10680, GREECE.
International Journal of Peptide and Protein Research, (1986) Vol. 28, No. 4, pp. 370-378.
CODEN: IJPPC3. ISSN: 0367-8377. Language: ENGLISH.
AB The enkephalin analog, H-Tyr-D-Thr-Gly-Phe-Δ3Pro-NH2 + HCl (VI)([D-Thr2, Δ3Pro5]-enkephalinamide), has been synthesized by conventional methods in solution and purified to homogeneity by reversed

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phase HPLC. The analog is a potent analgesic agent. For evaluation of some of its biological activity a related compound [D-Thr2, Thz5]-enkephalinamide (XI) was also synthesized in solution. Anti-diarrhea activity was evaluated in mice by the intravenous route for anti-DL-5-hydroxytryptophan (5-HTP) induced diarrhea activity. Analgesic activity was assayed by the method of Nilsen in mice using the intravenous route, and by a modified tail flick test in rats and the acetic acid writhing test in mice following subcutaneous administration. Within the constraints of the assays the two analogs are approximately equipotent. Both are less active than [D-Ala2, MePhe4, Met(O)ol]-enkephalinol (xii). Earlier receptor binding studies of compound XI indicated enhanced affinity for the μ receptor and little for the δ receptor. By comparison this may also be the case for compound VI.

=> s (tripeptide and neurodegenera?)
L41 21 FILE MEDLINE
L42 33 FILE HCAPLUS
L43 25 FILE EMBASE
L44 18 FILE BIOSIS
L45 14 FILE WPIDS

TOTAL FOR ALL FILES
L46 111 (TRIPEPTIDE AND NEURODEGENERA?)

=> dup rem l46
PROCESSING COMPLETED FOR L46
L47 51 DUP REM L46 (60 DUPLICATES REMOVED)

=> s l46 and (treat? or therap?)
L48 5 FILE MEDLINE
L49 12 FILE HCAPLUS
L50 8 FILE EMBASE
L51 5 FILE BIOSIS
L52 14 FILE WPIDS

TOTAL FOR ALL FILES
L53 44 L46 AND (TREAT? OR THERAP?)

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L54 26 DUP REM L53 (18 DUPLICATES REMOVED)

=> d 1-26 cbib abs

L54 ANSWER 1 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1
2004:269847 Document No. 140:297534 Nitric oxide synthase inhibitor neuroprotective agents. Yalpani, Manssur (USA). U.S. Pat. Appl. Publ. US 2004063612 A1 20040401, 27 pp. (English). CODEN: USXXCO. APPLICATION: US 2003-672257 20030926. PRIORITY: US 2002-PV414694 20020926.
AB The invention provides methods for **treating neurodegenerative** diseases with neuroprotective agents which inhibit nitric oxide synthase enzymes and in particular nitric oxide synthase III and can be used to **treat** Alzheimer's disease. Compds. of the invention include e.g. polyglutamate polymers, and arabinogalactan compds.

L54 ANSWER 2 OF 26 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
AN 2004-411526 [38] WPIDS
AB WO2004042079 A UPAB: 20040616
NOVELTY - Identifying (M1) a compound (C1) which induces the mitochondrial permeability transition (MPT) in proliferating cells, involves contacting

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a cell or cell extract with a compound, determining whether the compound binds to adenine nucleotide translocator (ANT), and determining whether the compound selectively induces the MPT in proliferating cells.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) screening (M2) several compounds to identify (C1), involves contacting a cell or cell extract with several compounds, determining whether any of the compounds bind to ANT, and if so, separately determining whether each of the several compounds selectively induces the MPT in proliferating cells;

(2) inducing MPT in a vertebrate, involves administering an (C1) identified by (M1) or (M2), or a pharmaceutical composition (PC) comprising an (C1) and a carrier, adjuvant and/or diluent, to the vertebrate;

(3) inducing apoptosis in proliferating mammalian cells, involves administering to the mammal an apoptosis-inducing amount of (C1), or (PC); and

(4) inhibiting angiogenesis in a mammal, involves administering to the mammal an angiogenesis-inhibiting amount of (C1), or (PC).

ACTIVITY - Antipsoriatic; Cytostatic; Thrombolytic; Neuroprotective; Nootropic; Vasotropic; Antiarthritic; Antirheumatic; Antiinflammatory; Dermatological; Immunosuppressive; Cerebroprotective; Cardiant; Antianginal.

In vivo analysis of the identified compound such as 4-(N-(S-glutathionylacetyl)amino)-phenylarsenoxide) (GSAO), which induces mitochondrial permeability transition in proliferating cells, for inhibiting tumor growth or cytostatic activity was as follows: female 7-9 week old SCID or C57B16/J mice were anesthetized by inhalation of isoflurane, the dorsal skin shaved and cleaned with ethanol, and a suspension of 2.5 multiply 106BxPC-3, HT1080 or LLC cells in 0.2 mL if PBS, or saline for LLC cells, was injected subcutaneously in the proximal midline. To SCID mice bearing BxPC-or HT1080 tumors, or C57B16/J mice bearing LLC tumors, GSAO was administered subcutaneously at the concentration of 10 mg/kg/day, and the growth of the tumor was observed. The result showed that the GSAO exhibited greater than 90 %, approximately 70 % or approximately 50 % inhibition of the rate of tumor growth, respectively. Thus the GSAO inhibited the growth of tumor in mice.

MECHANISM OF ACTION - Inhibition of tumor angiogenesis; inducer of apoptosis; inducer mitochondrial permeability transition in proliferating cells (claimed).

USE - (M1) is useful for identifying a compound which induces MPT in proliferating cells. The compound identified by (M1) is useful for inducing MPT in a vertebrate, and apoptosis in proliferating mammalian cells, and for inhibiting angiogenesis in a mammal (claimed). The compound identified by (M1) is useful for **treating** angiogenesis-dependent diseases, cellular proliferative diseases (e.g. psoriasis, IBD, malignancies, restenosis), inflammatory disorders such as rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome and other inflammatory eye disease, auto-immune diseases, blood vessel diseases such as ischaemic, completed stroke, acute myocardial infarction (primary and secondary), angina and venous thromboembolic disease following surgery, thrombosis, cancer, **neurodegenerative** disorders (e.g. Alzheimer's disease, Parkinson's disease), myelodysplastic syndromes, ischemia/reperfusion injury and organ transplant injury etc.

DESCRIPTION OF DRAWING(S) - The graph shows the effect of 4-(N-(S-glutathionylacetyl)amino)-phenylarsenoxide) (GSAO) in tumor growth or angiogenesis inhibition.

Dwg.7/23

L54 ANSWER 3 OF 26 MEDLINE on STN DUPLICATE 2

2003197927. PubMed ID: 12717677. [Glutathione in cognitive function and **neurodegeneration**]. El glutation en la funcion cognitiva y la

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neurodegeneracion. Cruz R; Almaguer Melian W; Bergado Rosado J A. (Centro Internacional de Restauracion Neurologica (CIREN), Ciudad de La Habana, Cuba.. reyniel@searchbug.com) . Revista de neurologia, (2003 May 1-15) 36 (9) 877-86. Ref: 135. Journal code: 7706841. ISSN: 0210-0010. Pub. country: Spain. Language: Spanish.

AB OBJECTIVE: To review the main findings on the glutathione role in cognitive function and synaptic plasticity processes, as well as, its involvement in neurotrophic and **neurodegenerative** events in rodents. DEVELOPMENT: The **tripeptide** glutathione and its related enzymes participate in the maintenance of oxidant homeostasis in aerobic cells. Oxidative damage to neuronal components underlies the molecular basis of **neurodegeneration** and brain aging. Several biomolecules with redox dependent activity are involved in the neuronal plasticity events that have a role in learning and memory functions. The maintenance of normal glutathione level is important for acquisition, but not consolidation, of spatial memory. Glutathione unavailability induces failures in hippocampal synaptic plasticity mechanisms, which are possibly related to a spatial memory deficit. On the other hand, several studies have suggested that the beneficial effects of neurotrophic **treatments** are mediated by the modulation of antioxidant defense mechanisms. In fact, nerve growth factor **treatment** to cognitively impaired rats stimulates glutathione reductase and can prevent the increases in glutathione peroxidase activity, pointing these enzymes as possible intracellular targets of neurotrophin actions on oxidant homeostasis. CONCLUSION: There is a closed link between glutathione metabolism and oxidant homeostasis, which is expressed in learning and synaptic plasticity deficits in conditions of low glutathione content, as well as, in **neurodegeneration** induced glutathione metabolism changes that can be prevented by neurotrophic **treatment**

L54 ANSWER 4 OF 26 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2003047732 EMBASE Emerging β-amyloid **therapies** for the **treatment** of Alzheimer's disease. Conway K.A.; Baxter E.W.; Felsenstein K.M.; Reitz A.B.. K.A. Conway, Drug Discovery Division, Johnson/Johnson Pharm. Res./Develop., Spring House, PA 19477, United States. kconway3@prdus.jnj.com. Current Pharmaceutical Design 9/6 (427-447) 2003.
Refs: 313.
ISSN: 1381-6128. CODEN: CPDEFP. Pub. Country: Netherlands. Language: English. Summary Language: English.

AB Alzheimer's Disease (AD) is a progressive **neurodegenerative** disorder marked by loss of memory, cognition, and behavioral stability. AD is defined pathologically by extracellular neuritic plaques comprised of fibrillar deposits of β-amyloid peptide (Aβ) and neurofibrillary tangles comprised of paired helical filaments of hyperphosphorylated tau. Current **therapies** for AD, such as cholinesterase inhibitors, **treat** the symptoms but do not modify the progression of the disease. The etiology of AD is unclear. However, data from familial AD mutations (FAD) strongly support the "amyloid cascade hypothesis" of AD, i.e. that **neurodegeneration** in AD is initiated by the formation of neurotoxic β-amyloid (Aβ) aggregates; all FAD mutations increase levels of Aβ peptide or density of Aβ deposits. The likely link between Aβ aggregation and AD pathology emphasizes the need for a better understanding of the mechanisms of Aβ production. This review summarizes current **therapeutic** strategies directed at lowering Aβ levels and decreasing levels of toxic Aβ aggregates through (1) inhibition of the processing of amyloid precursor protein (APP) to Aβ peptide, (2) inhibition, reversal or clearance of Aβ aggregation, (3) cholesterol reduction and (4) Aβ immunization.

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L54 ANSWER 5 OF 26 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2003247435 EMBASE The importance of glutathione in human disease. Townsend D.M.; Tew K.D.; Tapiero H.. D.M. Townsend, Department of Pharmacology, Fox Chase Cancer Center, 7701 Burholme Ave., Philadelphia, PA 19111, United States. dm_townsend@fccc.edu. Biomedicine and Pharmacotherapy 57/3 (145-155) 1 May 2003.
Refs: 102.
ISSN: 0753-3322. CODEN: BIPHEX. Pub. Country: France. Language: English. Summary Language: English.

AB Reduced glutathione (GSH) is the most prevalent non-protein thiol in animal cells. Its de novo and salvage synthesis serves to maintain a reduced cellular environment and the **tripeptide** is a co-factor for many cytoplasmic enzymes and may also act as an important post-translational modification in a number of cellular proteins. The cysteine thiol acts as a nucleophile in reactions with both exogenous and endogenous electrophilic species. As a consequence, reactive oxygen species (ROS) are frequently targeted by GSH in both spontaneous and catalytic reactions. Since ROS have defined roles in cell signaling events as well as in human disease pathologies, an imbalance in expression of GSH and associated enzymes has been implicated in a variety of circumstances. Cause and effect links between GSH metabolism and diseases such as cancer, **neurodegenerative** diseases, cystic fibrosis (CF), HIV, and aging have been shown. Polymorphic expression of enzymes involved in GSH homeostasis influences susceptibility and progression of these conditions. This review provides an overview of the biological importance of GSH at the level of the cell and organism. .COPYRGT. 2003 Editions scientifiques et medicales Elsevier SAS. All rights reserved.

L54 ANSWER 6 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 3

2002:609523 Document No. 137:155181 Synthesis of **tripeptides** and **tripeptide** derivatives for the **treatment** of **neurodegenerative** diseases. Rapin, Jean; Witzmann, Hans Klaus; Grumel, Jean-Marie; Gonella, Jacques (Tell-Pharm Ag, Switz.). Ger. Offen. DE 10105041 A1 20020814, 12 pp. (German). CODEN: GWXXBX. APPLICATION: DE 2001-10105041 20010205.

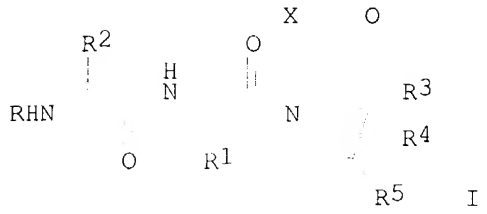
AB The invention concerns the use of **tripeptide** derivs. [e.g., H-Gly-Phe-Pro-NH2 (I)] for the **treatment** of **neurodegenerative** disease, such as Alzheimer's disease. Thus, Boc-Phe-OH [Boc = (CH3)3OC(O)] was coupled with TFA.H-Pro-NH2 to give a dipeptide, which was N-deprotected and converted to its TFA salt for coupling with Boc-Gly-OH; the resulting protected **tripeptide** was N-deprotected and converted to its HCl salt. The blood-brain partition coeffs. of I and seventeen similar **tripeptides** were given. The plasma half-life of 14C-labeled I.HCl was determined in rats (no data). Using a rat model of Alzheimer's disease, results of **treatment** with I showed retention of learned behavior in a five-day test of pole-climbing at a signal to avoid shock. Examination of subject brains revealed increase dendrite development in the hippocampus.

L54 ANSWER 7 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 4

2002:591566 Document No. 137:135103 **Tripeptide** derivatives for **treatment** of **neurodegenerative** diseases. Rapin, Jean; Witzmann, Hans Klaus; Grumel, Jean-Marie; Gonella, Jacques (Tell-Pharm A.-G., Switz.). Ger. Offen. DE 10105039 A1 20020808, 10 pp. (German). CODEN: GWXXBX. APPLICATION: DE 2001-10105039 20010205.

GI

Searched by: Mary Hale 571-272-2507 REM 1D86



AB The invention discloses the use of **tripeptide** derivs. for **treatment** of **neurodegenerative** diseases. The **tripeptide** derivs. are I [X = OH, C1-5 alkoxy, NH2, NH(C1-5 alkyl), N(C1-5 alkyl)2; R = (preferably) cinnamoyl; R1 = group derived from Phe, Tyr, Trp, Pro, Ala, Val, Leu or Ile; R2 = group derived from Gly, Ala, Ile, Val, Ser, Thr, His, Arg, Lys, Pro, Glu, Gln, pGlu, Asp or Asn; R3, R4 = H, OH, C1-5 alkyl, C1-5 alkoxy, provided that R3 and R4 are not both OH or C1-5 alkoxy; R5 = H, OH, C1-5 alkyl, C1-5 alkoxy], or a pharmaceutically compatible salt. Cinnamoyl-Gly-L-Phe-L-Pro-NH2 was tested in an Alzheimer's disease model.

L54 ANSWER 8 OF 26 MEDLINE on STN DUPLICATE 5

2002454942. PubMed ID: 12213603. Glutathione, iron and Parkinson's disease. Bharath Srinivas; Hsu Michael; Kaur Deepinder; Rajagopalan Subramanian; Andersen Julie K. (Buck Institute For Age Research, 8001 Redwood Boulevard, Novato, CA 94945, USA.) Biochemical pharmacology, (2002 Sep) 64 (5-6) 1037-48. Ref: 146. Journal code: 0101032. ISSN: 0006-2952. Pub. country: England: United Kingdom. Language: English.

AB Parkinson's disease (PD) is a progressive **neurodegenerative** disease involving **neurodegeneration** of dopaminergic neurons of the substantia nigra (SN), a part of the midbrain. Oxidative stress has been implicated to play a major role in the neuronal cell death associated with PD. Importantly, there is a drastic depletion in cytoplasmic levels of the thiol **tripeptide** glutathione within the SN of PD patients. Glutathione (GSH) exhibits several functions in the brain chiefly acting as an antioxidant and a redox regulator. GSH depletion has been shown to affect mitochondrial function probably via selective inhibition of mitochondrial complex I activity. An important biochemical feature of **neurodegeneration** during PD is the presence of abnormal protein aggregates present as intracytoplasmic inclusions called Lewy bodies. Oxidative damage via GSH depletion might also accelerate the build-up of defective proteins leading to cell death of SN dopaminergic neurons by impairing the ubiquitin-proteasome pathway of protein degradation. Replenishment of normal glutathione levels within the brain may hold an important key to **therapeutics** for PD. Several reports have suggested that iron accumulation in the SN patients might also contribute to oxidative stress during PD.

L54 ANSWER 9 OF 26 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

2003:326949 Document No.: PREV200300326949. ELEVATING MITOCHONDRIAL GLUTATHIONE LEVELS BY gamma - GLUTAMYLCYSTEINE ETHYL ESTER PROTECTS BRAIN CELLS AGAINST PEROXYNITRITE - INDUCED OXIDATIVE STESS: IMPLICATIONS FOR ALZHEIMER'S DISEASE. Drake, J. [Reprint Author]; Aksenova, M. [Reprint Author]; Butterfield, D. A. [Reprint Author]. Dept Chemistry, Center of Membrane Sciences, Sanders-Brown Center on Aging, Univ Kentucky, Lexington, KY, USA. Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002) Vol. 2002, pp. Abstract No. 784.9. http://sfn.scholarone.com. cd-rom.
Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience.

Searched by: Mary Hale 571-272-2507 REM 1D86

Orlando, Florida, USA. November 02-07, 2002. Society for Neuroscience. Language: English.

AB Mitochondria are important participants in the regulation of the redox status of the neuron, and if compromised by oxidative stress, they may direct neuronal death either by apoptosis or necrosis. Lacking catalase, mitochondria depend on glutathione (GSH) as an endogenous protectant against H2O2 and other ROS. Because mitochondria lack the enzymes needed to synthesize GSH, this **tripeptide** must be transported into the mitochondria. Therefore, increasing GSH levels in the mitochondria may prove to be an important **therapeutic** approach to preventing neuronal death caused by oxidative stress. We have examined the ability of gamma-glu-cys-ethyl ester (GCEE), in-vitro and in-vivo, to protect mitochondria against ONOO-induced oxidative stress. GCEE increases GSH by providing the limiting substrate of GSH biosynthesis,gamma-glu-cys, thereby bypassing the feedback inhibition of gamma-glutamylcysteine synthetase. GCEE-**treated** synaptosomes were less susceptible to ONOO-induced mitochondrial damage as assessed by protein carbonyl measurement, 3-NT formation, measurements of mitochondrial potential, and by mitochondrial swelling. Hippocampal neuronal cell cultures exposed to ONOO-or AAPH were protected against cell death and mitochondrial dysfunction as assessed by the MTT reduction assay. These experiments suggest that GCEE is effective in increasing mitochondrial GSH and protecting neurons against oxidative stress, pointing to a potential **therapeutic** role in attenuating oxidative stress in **neurodegenerative** diseases associated with mitochondrial dysfunction.

L54 ANSWER 10 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 6

2001:545831 Document No. 135:121188 Vaccines against **neurodegenerative** disorders. Srivastava, Pramod K. (University of Connecticut Health Center, USA). PCT Int. Appl. WO 2001053457 A2 20010726, 47 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US1665 20010118. PRIORITY: US 2000-489219 20000121.

AB The present invention relates to pharmaceutical compns. comprising antigenic mols. for use as vaccines for the **treatment** and prevention of **neurodegenerative** disorders and diseases, such as Alzheimer's Disease. The invention further relates to methods for the use of such pharmaceutical compns. as immunotherapeutic agents for **treating** and protecting against such **neurodegenerative** disorders and disease.

L54 ANSWER 11 OF 26 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN

AN 2001-273585 [28] WPIDS

CR 2001-367218 [38]

AB WO 200125486 A UPAB: 20030828

NOVELTY - Identifying a test compound (I) that binds to a target RNA molecule, comprising contacting a dye-labeled target RNA molecule with substantially one type of (I) attached to a solid support, thereby providing a dye-labeled target RNA:support-attached (I) complex and determining the structure of the substantially one type of (I) of the RNA:(I) complex, is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a compound (C) selected from the group consisting of:

(1) H2N-(L)Lys-(D)Lys-(L)Asn-OH;
(2) H2N-(L)Lys-(D)Lys-(D)Asn-OH;
(3) H2N-(L)Lys-(L)Lys-(L)Asn-OH;
(4) H2N-(L)Arg-(D)Lys-(L)Asn-OH;
(5) H2N-(L)Arg-(D)Lys-(L)Val-OH;
(6) H2N-(L)Arg-(D)Lys-(L)Arg-OH;
(7) H2N-(L)Thr-(D)Lys-(L)Asn-OH; and

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(8) H2N-(D)Thr-(D)Lys-(L)Phe-OH.

ACTIVITY - Nootropic; neuroprotective; immunosuppressive; antiarteriosclerotic; hemostatic; cytostatic; antidiabetic; anorectic; antiparkinsonian; anti-human immunodeficiency virus (HIV); virucide; hepatotropic; antiinflammatory; protozoacide; antibacterial; antidiarrheic.

MECHANISM OF ACTION - Displaces ligand of target RNA (claimed); inhibits protein-RNA or RNA-RNA interaction.

Different amounts of **tripeptide** ID1 were added during transfection of pSV2-Tat and pAL plasmids (expressing first exon of Tat protein and luciferase enzyme, respectively) into HL3T1 cells. Increasing amounts of **tripeptide** ID1 resulted in a decrease of CAT (undefined) activity while luciferase activity was not affected. In the presence of 700 nM concentration of **tripeptide** ID1, more than 90% of Tat-transactivation was inhibited. The results showed that **tripeptide** ID1 binds trans-activation response region RNA (TAR RNA) and inhibits Tat-TAR interactions in vivo, and hence suitable for preventing or **treating** human immunodeficiency virus (HIV) infections or acquired immunodeficiency syndrome (AIDS) in patients.

USE - (I) is useful for forming a target RNA:test compound complex, for increasing or decreasing the production of a protein by contacting a target mRNA molecule that encodes the protein with (I), and for **treating** or preventing a disease e.g., amyloidosis, hemophilia, Alzheimer's disease, atherosclerosis, cancer, giantism, dwarfism, hypothyroidism, hyperthyroidism, inflammation, cystic fibrosis, autoimmune disorders, diabetes aging, obesity, **neurodegenerative** disorders, Parkinson's disease, human immunodeficiency virus (HIV) infection, acquired immunodeficiency syndrome (AIDS), human T-cell leukemia, simian immunodeficiency virus (SIV) infection, feline immunodeficiency virus (FIV) infection, feline leukemia, hepatitis B, hepatitis C, Dengue fever, malaria, rotavirus infection, severe acute gastroenteritis, diarrhea, encephalitis, hemorrhagic fever, syphilis, legionella, whooping cough, gonorrhea, sepsis, influenza, pneumonia, tinea infection, Candida infection and meningitis, whose progression is associated with in vivo binding of (I) to target RNA (claimed).

ADVANTAGE - The method is fast and efficient in screening combinatorial compound libraries for molecules that bind to RNAs and potentially disrupt protein-RNA and RNA-RNA interactions.

Dwg.0/5

L54 ANSWER 12 OF 26 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN

AN 2001-244300 [25] WPIDS

AB WO 200114412 A UPAB: 20010508

NOVELTY - Hydrazinylcarbonyl substituted heterocyclic compounds (I) that mimic beta -strands and/or beta -sheets, based on amino aromatic derivatives, are new.

DETAILED DESCRIPTION - Hydrazinylcarbonyl substituted heterocyclic compounds of formula (I) that mimic beta -strands and/or beta -sheets, based on amino aromatic derivatives, are new.

R1 = H, 2-20C acyl, 1-20C alkyl or 6-20 aryl, or an amino acid or peptide;

R2 = H, 1-20C alkyl or 6-20C aryl;

W' = H, F or NH-CO-CO-Z;

X = O, S, NR3, CR4=N, N=CR4= or CR4=CR5;

R3 = R2 or 2-20C acyl;

R4, R5 = H, alkyl, halo, nitro, carboxyl, amino, alkyl sulfone, aryl sulfone, alkyl sulfoxide, aryl sulfoxide, sulfonic acid, sulfonate salt or sulfonamide; or

R4 + R5 = form a ring;

Y = O or S; or

YR2 = halo

Z = OR6 or NR7R8; and

R6 - R8 = R1.

INDEPENDENT CLAIMS are also included for the following:

(1) a peptide, protein or a peptidomimetic compound incorporating (I);

(2) (I) combined with an agent to cause that agent to mimic beta -strands, block beta dimerization of proteins, block protein-protein beta -sheet interaction, or to interact with a protein by beta -sheet formation;

(3) a preparation comprising (I) in a carrier;

(4) a peptide synthesis process (M1) which involves attaching one amino acid to another on a peptide chain involves attaching to the N-terminus (of the amino acid to be added) a protecting group comprising Fmoc asterisk , causing the amino acid to form a peptide linkage with the other amino acid or peptide such that the protecting group that had been attached to the amino acid in the previous step is at the N-terminus of the growing peptide chain;

(5) an N-terminally protected amino acid having a formula P-AA, in which AA is an amino acid and P is (2,7-di-tert-butylfluorenylmethyloxycarbonyl (Fmoc asterisk);

(6) an N-terminal protected peptide having the formula P-(AA)n, in which AA is an amino acid, P is Fmoc asterisk and n is 2 or more; and

(7) identifying (M2) compounds which participate in beta -sheet interaction with a protein involves providing a protein, test compound and a compound which mimics (I), non-covalently binding the protein to (I) to form a complex, contacting test compound with the complex and determining the dissociation of the complex.

ACTIVITY - Neuroleptic; cytostatic; nootropic; anticonvulsant; neuroprotective.

MECHANISM OF ACTION - Mimics and/or modulates beta -sheet interactions.

No supporting data is given.

USE - (I) may be combined with a compound (a peptide, protein or a peptidomimetic compound) causes dimerization of a compound that is capable of dimerizing due to beta -sheet interactions. (I) is also useful for **treating** a disease or disorder in a human or animal patient, such as cancer in which (I) mimics a beta -sheet and binds with a Ras oncoprotein or a Ras-binding domain of serine/kinase c-Raf1 (Raf). (I) is also useful for **treating** a **neurodegenerative** disease such as Huntington's disease or schizophrenia, in which proteins form oligomeric compounds and (I) mimics a beta -sheet (preferably, mimics a polyglutamine beta -sheet aggregate) and disrupts the formation of such oligomeric aggregates. (I) thus is also useful for **treating** Alzheimer's disease where (I) mimics beta -sheet and binds to beta -amyloid aggregates and block beta -amyloid fibril growth (claimed).

DESCRIPTION OF DRAWING(S) - An unfolded Hao-containing peptide folding into an antiparallel beta -sheet or, alternatively, a parallel beta -sheet.

Dwg.11/12

L54 ANSWER 13 OF 26 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
AN 2001-367073 [38] WPIDS
AB WO 200110457 A UPAB: 20010711

NOVELTY - A novel composition for inhibiting transcriptional activation by interrupting dimerization of a transcriptional activator comprises a peptide (I) in amide form.

DETAILED DESCRIPTION - A novel composition for inhibiting transcriptional activation by interrupting dimerization of a transcriptional activator comprises a peptide (I) in amide form of formula X1X2X3-NH2.

X1, X2, X3 = any amino acid, provided the peptide is not Gly-Pro-Gly-NH2.

INDEPENDENT CLAIMS are include for:

(1) a composition comprising a peptide (I) for inhibiting transcriptional repression by interrupting the association of a transcriptional repressor with a transcriptional activator, inhibiting assembly of a bacterial holotoxin by preventing the association of a toxin protein subunit in a protein complex; inhibiting actin polymerization by preventing the association of an actin subunit in a protein complex and inhibiting aggregation of a beta -amyloid peptide by preventing the association of a beta -amyloid subunit in a protein complex, inhibiting assembly of a tubulin complex by preventing the association of a tubulin subunit in a protein complex;

(2) a method of inhibiting transcriptional activation comprising providing a cell with peptide (II) of formula X1X2X3-NH2 where X1, X2, X3 are any amino acid, inhibiting transcriptional repression comprising providing a cell with (II), inhibiting assembly of a bacterial holotoxin using (II), inhibiting actin polymerization, inhibiting beta -amyloid peptide aggregation, inhibiting tubulin polymerization using (II);

(3) a method of preparing a pharmaceutical comprising:

(a) selecting and obtaining a peptide agent that corresponds to a region of a protein involved in a protein-protein interaction;

(b) identifying in the peptide agent obtained in step (a) a characteristic selected from (i) the ability to bind protein, (ii) the ability to prevent protein polymerization and (iii) the ability to modulate a cellular response; and

(c) incorporating the peptide agent identified in step (b) into a pharmaceutical;

(4) a composition comprising a peptide (III) in amide form of formula X1X2X3-R for inhibiting transcriptional activation by interrupting dimerization of a transcriptional activator where X1X2X3 are any amino acid, provided the peptide is not Gly-Pro-Gly-NH2 and R is a modulation group attached to the carboxy-terminus of the peptide comprising an amide group or other moiety having a similar charge and steric bulk;

(5) a composition comprising a peptide (III) for inhibiting transcriptional repression by interrupting the association of a transcriptional repressor with a transcriptional activator;

(6) a composition comprising a peptide (III) for inhibiting assembly of a bacterial holotoxin by preventing the association of a toxin protein subunit in a protein complex, inhibiting actin polymerization by preventing the association of an actin subunit in a protein complex or inhibiting actin polymerization by preventing the association of an actin subunit in a protein complex;

(7) a composition comprising peptide (III) for inhibiting assembly of a tubulin complex by preventing the association of a tubulin subunit in a protein complex;

(8) a composition for inhibiting transcriptional activation, transcriptional repression, assembly of a bacterial holotoxin, actin polymerization, aggregation of a beta -amyloid peptide and assembly of a tubulin complex comprising a peptide (IV) of formula X4X5X6X7X8X9X10X1X2X3-R where X4-X10 is any amino acid, where any 1-7 amino acids is absent and R is a modulation group attached to the carboxy-terminus of the peptide comprising an amide group or other moiety having a similar charge and steric bulk;

(9) a method of inhibiting transcriptional activation comprising providing a cell with a peptide (III) or (IV);

(10) a method of inhibiting transcriptional repression comprising providing a cell with a peptide (III) or (IV);

(11) a method of inhibiting assembly of a bacterial holotoxin comprising providing a cell with peptide (III) or (IV);

(12) a method of inhibiting actin polymerization comprising providing a cell with peptide (III) or (IV);

(13) a method of inhibiting beta -amyloid peptide aggregation comprising providing a cell with peptide (III) or (IV); and

(14) a method for inhibiting tubulin polymerization comprising

providing a cell with peptide (III) or (IV);

(15) a method for **treating** and preventing a human disease comprising:

(a) identifying an individual that over expresses NFkappaB or is at risk of over-expressing NFkappaB; and

(b) administering a peptide (II);

(16) a method for **treating** and preventing a human disease comprising:

(a) identifying an individual that over expresses IkappaB or is at risk of over-expressing IkappaB; and

(b) administering a peptide (II); and

(17) a method of **treating** human disease comprising:

(i) identifying an individual in need of an agent that inhibits a protein-protein interaction; and

(ii) administering a composition comprising peptide (IV).

ACTIVITY - Neuroprotective; nootropic; cytostatic; antiviral; antiinflammatory; cerebroprotective; anticonvulsant.

MECHANISM OF ACTION - The peptides inhibit protein-protein interactions necessary for protein polymerization and assembly of supra molecular protein complexes, i.e. the peptides are protein-protein polymerization inhibitors and protein complex formation inhibitors.

USE - The peptides are useful for modulating the protein-protein interactions necessary for protein polymerization and the assembly of supramolecular protein complexes. The modified peptides of formula (I) - (IV) are useful for inhibiting transcriptional activation, transcriptional repression, assembly of a bacterial holotoxin, actin polymerization, aggregation of a beta -amyloid peptide and assembly of a tubulin complex. The peptides are useful for treating or preventing human diseases, e.g. inflammatory diseases and immune disorders, which are associated with aberrant regulation of the NFkappaB or IkappaB complex. The peptides are also useful for treating or preventing various forms of cancer e.g. leukemia, prostate cancer and colon cancer, as well as neurodegenerative diseases such as Alzheimer's disease, stroke, Huntington's disease and scrapie and other prion-related diseases. The small peptides referred to as protein polymerization inhibitors (PPI) are useful in the manufacture of biotechnological tools and pharmaceuticals for the study and prevention and treatment of human disease. The peptides are also capable of inhibiting or preventing the assembly of viral capsid proteins and thus can be used for treating or preventing viral infections such as HIV infection and also for preventing the toxic effects of bacterial holotoxins. The peptide agents can be administered as therapeutics or prophylactics and may be used both for the treatment and/or prevention of disease.

Dwg.0/5

L54 ANSWER 14 OF 26 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN

AN 2001-440210 [47] WPIDS

AB US 6235929 B UPAB: 20010822

NOVELTY - **Tripeptide** ketoamide derivatives and their salts are new.

DETAILED DESCRIPTION - **Tripeptide** ketoamide derivatives of formula (I) and their salts are new. M1-AA1-AA2-AA3-CO-NR3R4 (I)

M1 = H, NH2CO-, NH2CS-, NH2SO2-, XNHCO-, X2NCO-, XNHCS-, X2NCS-, XNHSO2-, X2NSO2-, XCO-, XCS-, XSO2-, XOCO- or XOCS-;

X = 1-10C (fluoro)alkyl (optionally substituted by J), 1-adamantyl, 9-fluorenyl, phenyl or naphthyl (optionally substituted by up to 3 of K), or 1-10C alkylphenyl, 1-10C alkyldiphenyl or 1-10C alkylphenoxy (all optionally substituted by K);

J = halo, COOH, OH, CN, NO2, NH2, 1-10C alkoxy, 1-10C alkylamine, 2-12C dialkylamine, 1-10C alkyl-OCO-, 1-10C alkyl-OCONH- or 1-10C alkylthio;

K = halo, 1-10C (perfluoro)alkyl, 1-10C alkoxy, NO2, CN, OH, COOH,

NH2, 1-10C alkylamino, 2-12C dialkylamino, 1-10C acyl, 1-10C alkoxy-CO or 1-10C alkylthio;

AA1, AA2 = D- or L-alanine, valine, leucine, isoleucine, glycine, serine, aspartic acid or glutamic acid;

AA3 = aspartic acid or glutamic acid;

R3 = 2-3C alkylphenyl, 3-20C cycloalkylphenyl, 1-20C alkylphenyl (substituted by up to 3 of K), 3-20C cycloalkylphenyl (substituted by K), NH-CH2CH2-(4-hydroxyphenyl) or NH-CH2CH2-(3-indolyl); and

R4 = H, 3-20C alkyl, cycloalkyl, 1-20C alkylphenyl (optionally substituted by up to 3 of K), 3-20C cycloalkylphenyl (optionally substituted by K), NHCH2CH2-(4-hydroxyphenyl) or NHCH2CH-2-(3-indolyl).

ACTIVITY - Vasotropic; cerebroprotective; nootropic; neuroprotective; anticoagulant; thrombolytic; antirheumatic; antiarthritic; antiinflammatory; virucide; cardiant; cytostatic; osteopathic.

MECHANISM OF ACTION - Serine protease inhibitor; cysteine protease inhibitor.

Compounds (I) had Ki values for inhibition of Calpain II of 22-350 nM.

USE - (I) are useful for **treating neurodegenerative** diseases (including ischemia, stroke and Alzheimer's disease), as anticoagulants and for **treating** thrombosis. (I) are also useful for **treating** emphysema, adult respiratory distress syndrome, rheumatoid arthritis, pancreatitis, viral infections, muscular dystrophy, myocardial tissue damage, tumor metastasis and bone resorption. Dwg.0/0

L54 ANSWER 15 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 7

2000:53392 Document No. 132:117561 Use of prenyltransferase inhibitors for preparing a medicine for **treating** pathologies resulting from heterotrimeric G protein membrane fixation. Prevost, Gregoire; Lonchampt, Marie-Odile (Societe de Conseils de Recherches et d'Applications Scientifiques (S.C.R.A.S, Fr.). PCT Int. Appl. WO 2000002558 A1 20000120, 58 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (French). CODEN: PIXXD2. APPLICATION: WO 1999-FR1611 19990705. PRIORITY: FR 1998-8730 19980708.

AB Prenyltransferase inhibitors are used for preparing a medicine for **treating** pathologies resulting from prenylation of the γ subunit of G protein. Said diseases comprise in particular diseases related to the following biol. functions or disorders: smell, taste, light perception, neurotransmission, **neurodegeneration**, endocrine and exocrine gland functioning, autocrine and paracrine regulation, blood pressure, embryogenesis, viral infection, immunol. functions, diabetes, and obesity.

L54 ANSWER 16 OF 26 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN

AN 2000-442360 [38] WPIDS

AB WO 200035942 A UPAB: 20000811

NOVELTY - New substituted heterocyclic acyl-tri- or tetra-peptide compounds are disclosed.

DETAILED DESCRIPTION - Substituted heterocyclic acyl-tri- or tetra-peptide compounds of formula (I) and their salts are new:

A1 = an amino acid residue selected from Cha, Leu, Ile, Arg, Lys, Phe (optionally substituted), Tyr, or Trp;

A2 = an amino acid residue selected from Lys, Orn, Arg and homo Arg;

A3 = amino acid residue selected from Phe (optionally substituted), homo Phe, Tyr, Trp, phgly, 2-Thala, 3-Thala, Cha, Leu, Ile, Asn, Gln, Arg,

homo Arg, Orn or Lys;
X = CO, CS, or SO2;
Y = optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, or optionally substituted heteroarylethylenyl, optionally substituted arylacrylamidoheteroaryl, optionally substituted heteroarylacrylamidoheteroaryl, provided that Y is not pyrrolidinyl, phenyl or 2-aminophenyl;
Z' = NH2, NH-alkyl, NH-aralkyl, or Arg-NH2.
All amino acids are in the L configuration.
ACTIVITY - Antiinflammatory.; Vulnerary; Cardiant; Cerebroprotective; Vasotropic; Antianginal; Antiarterosclerotic; Cytostatic; Osteopathic; Neuroprotective.
MECHANISM OF ACTION - Thrombin receptor agonists/antagonists.
As an example of agonists, (I) where Y = bromopyridine-3-yl; A1 - Cha; A2 = Arg; A3 = Phe; X = CO; Z = NH2, has EC50 = 0.46M for platelet aggregation and IC50 = 1.7M for binding at the thrombin receptor.
As an example of antagonists, (I) where Y = 5-(Cl-cinnamido)triazol-3-yl; A1 = Cha; A2 = Arg; A3 = Phe; X = CO; Z = NH2 has IC50 = 3.6M for inhibition of platelet aggregation induced by thrombin and IC50 = 1.4M for binding of the thrombin receptor.
USE - The compounds can be used to **treat** a condition mediated by modulation of the thrombin receptor in a subject (claimed). They can be used for e.g. wound healing, tissue repair, myocardial infarction, stroke, restenosis, angina, atherosclerosis, ischemic attacks, inflammation, cancer, osteoporosis or **neurodegenerative** disorders (claimed).
Dwg.0/0

L54 ANSWER 17 OF 26 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
AN 2000-400034 [34] WPIDS
AB WO 200031120 A UPAB: 20000718
NOVELTY - A novel composite (A) comprises an oxidized glutathione-based compound (GBC) and a metal material in a ratio of 3000:1 to 1:1, where the metal material is selected from platinum and palladium.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(1) a method for stabilizing a disulfide bond of an oxidized GBC, comprising interacting the oxidized GBC with a metal material comprising a metal selected from platinum and palladium;
(2) a method of stimulating endogenous production of cytokines and hemopoietic factors comprising introducing to a mammalian body, a composite comprising an oxidized GBC and a metal material in a ratio of 3000:1 to 1:1 where the metal material comprises a metal selected from platinum and palladium, to obtain a **therapeutic** effect;
(3) a method of enhancing and prolonging the ability of an oxidized GBC to stimulate endogenous production of cytokine and hemopoietic factors, comprising interacting the oxidized GBC with a metal material in a ratio of 3000:1 to 1:1 where the metal material comprises platinum or palladium;
(4) a method for **treating** a subject having a disease comprising administering a composite comprising an oxidized GBC and a metal material in a ratio of 3000:1 to 1:1 to stimulate endogenous production of cytokines and/or hemopoietic factors or both, to obtain a **therapeutic** effect, where the metal material comprises platinum or palladium; and
(5) a medicinal agent regulating endogenous production of cytokines and hemopoietic factors and/or reproducing the cytokines' effects, thus providing regulation of processes of metabolism, proliferation, differentiation and apoptosis induction in normal, tumor- and/or virus-transformed cells containing a composite as in (A) as an active principle.
ACTIVITY - Cytostatic; tuberculostatic; hepatotropic;

antiinflammatory; virucide; antibacterial; immunosuppressive; anti-HIV; immunostimulant; antiallergic; nephrotropic; antirheumatic; antiarthritic; dermatological; vasotropic; cerebroprotective; cardiant; nootropic; neuroprotective; antiparkinsonian; anticonvulsant; neuroleptic; antiarteriosclerotic.

MECHANISM OF ACTION - Stimulates endogenous production of cytokines and hematopoeitic factors.

Oxidized glutathione (GSSG) and GSSG.Pt were evaluated for their effect on cytokine production by human peripheral blood mononuclear leukocytes (hPBMLs) in vitro. The results showed that the GSSG.Pt impact on the hPBMLs in vitro was manifested with considerable stimulation of a wider cytokine range release into culture media considering their reciprocal regulative effect, and thereby, it confirmed the GSSG.Pt stimulatory and regulatory effect on the natural cytokine-producing capacity of the human blood cells.

USE - The GBC composites can be used to stimulate endogenous production of cytokines and hematopoietic factors (claimed). They can be used for **treating** oncological, infectious, immunological, ischemic, **neurodegenerative**, metabolic, endocrinal and other diseases (claimed). In particular they can be used for **treating** e.g. lung cancer, melanoma, cerebral tumors, colorectal cancer, breast cancer, prostate cancer, ovarian cancer, acute lymphoblastic leukosis, acute myeloblastic leukosis, tuberculosis, viral hepatitis B, viral hepatitis C, mixed infections (HBV and HCV), herpes, meningitis (sepsis), peritonitis, acute pancreatitis, suppurative post-surgery sequalae, AIDS, immunosuppressions of infectious, radiation and toxic origin, glomerulonephritis, rheumatoid arthritis, collagenosis, systemic lupus erythematosis, allergic conditions, ischemic cerebral conditions, ischemic heart disease, Alzheimer's disease, Parkinson's disease, hereditary (Huntington's) chorea, amyotrophic lateral sclerosis, neuro-AIDS, demyelinating diseases, narcotic abstinence, cerebral hypoxia, manic-depressive psychosis, schizophrenia, atherosclerosis, or hypothalamic-hypophysial-ovarian function disorder (claimed). They can also be used for regulating proliferation in normal cells, regulating differentiation in normal cells, and inducing apoptosis of transformed cells (claimed). They can also be used for **treating** e.g. peritonitis, extra hazardous infections of viral origin (e.g. Rift Valley fever) or bacterial origin (e.g. tularemia), diabetes type (I) or diabetes type (II) (claimed).

ADVANTAGE - The compositions provide GBCs having a stabilized disulfide bond and a longer drug half-life time. The time-concentration GSSG curves and activity changes for enzymes participating at the GSSG metabolism after the GSSG.Pt and GSSG i.v. introduction in different doses were studied in mice.

Dwg.0/22

L54 ANSWER 18 OF 26 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
AN 2000-171129 [15] WPIDS
AB WO 200002904 A UPAB: 20000323

NOVELTY - Matrix metalloproteinase inhibitor peptides containing the sequence Pro-Leu-Ama (NHOH)- are new.

DETAILED DESCRIPTION - Compounds containing aminomalonic acid derivatives and their peptide backbone modified derivatives of formulae (I)-(VI) and their salts are new:

R1 = N-protecting group (e.g. tert-butyloxycarbonyl), acetyl, Co-lower alkyl, CH2-aryl, natural amino acid, lower alkyl, aryl, H, or optionally spacer linked such as a synthetic or natural peptide, glycoprotein, a solid or macromolecular product used for chromatolographical procedures;

R2 = NH-D-C(Ph)-CH2, NH-L-C(Ph)-CH3, N(lower alkyl)2, NH-lower alkyl, NH-aryl, natural amino acid, lower alkyl ester of an amino acid, O-lower alkyl, NHOH or OH, or optionally spacer linked: such as synthetic or

natural peptide, glycoprotein, solid or macromolecular product used for chromatoraphical procedures; or R4;

Ccc = optionally with abounded residue Rz; or Z;

R3 = lower alkyl or side chain of natural amino acid, or R4;

R7-R9 = H, alkyl, aryl, OH, CO-lower alkyl, O-lower alkyl, O-CH2-aryl, O-aryl, or cyclopropyl, cyclopentyl, cyclohexyl, a 5- or 6-membered aromatic or aliphatic N-heterocyclic ring which is attached via the N-atom or via a C-atom and (a) optionally contains N, O and/or S as an additional ring member and (b) is optionally benzofused or optionally substituted on one or more other C-atoms by lower alkyl, aryl and/or oxo; or optionally spacer linked: such as synthetic or natural peptide, glycoprotein, solid or macromolecular product used for chromatographical procedures;

n = 0-5;

R10 = R2, R4 or (CH2)mR4;

m = 0-6;

R4 = H, alkyl, aryl, OH, O-lower alkyl, O-CH2-aryl, O-aryl, NH-CO-aryl, NH-CO-NH-aryl, NH-CO-CH2-aryl or NH-COR5; NH2, NH-lower alkyl, N(lower alkyl)2, N(lower alkyl 1) (lower alkyl 2), NH aryl, N(aryl)2, N(aryl 1) (aryl 2), N(lower alkyl)3+, N(aryl3+; or cyclopropyl, cyclopentyl, cyclohexyl, a 5- or 6-membered aromatic or aliphatic N-heterocycle which is attached via the N-atom or via a C-atom and: (a) optionally contains N, O and/or S as an additional ring member, and (b) is optionally benzofused or optionally substituted on oen or more other C-atoms by lower alkyl, aryl and/or oxo; or an optionally spacer linked: such as synthetic or natural peptide, glycoprotein, a solid or macromolecular product used for chromatographical procedures;

Z = OH, O-lower alkyl, NHOH, N(CH3)OH, NHO-CH3 or NHO-lower alkyl;

Q = (CH2)m, O-(CH2)m, CO(CH2)m, (CH2)mP, O-(CH2)m-P, or CO-(CH2)m-P;

P = cyclopropyl, cyclopentyl, cyclohexyl, 5- or 6-membered aryl, or a 5- or 6-membered aromatic or oliphatic N-heterocycle which is attached via the N-atom or via a C-atom and: (a) optionally contains N, O and/or S as an additional ring member, and (b) is optionally benzofused or optionally substituted on one or more other ring C-atoms by lower alkyl, aryl and/or oxo; lower = 1-6C; aryl = phenyl optionally substituted by lower alkyl, O-lower alkyl and/or halo; spacer = alkyl, amino alkyl, carboxyalkyl up to 12 C or combinated forms, peptides or saccharides;

R5 = R1-proline, lower alkyl, aryl or cyclopropyl, cyclopentyl, cyclohexyl, a 5- or 6-membered aromatic or aliphatic N-heterocycle which is attached via the N-atom or via a C-atom, and: (a) optionally contains N, O and/or S, and (b) is optionally benzofused or optionally substituted on one or more other C-atoms by lower alkyl, aryl and/or oxo; or an optionally spacer linked: synthetic or natural peptide, glycoprotein, a solid or macromolecular product used for chromatographical procedures;

Aaa, Bbb = peptide bound natural amino acid;

Ccc = peptide bound natural amino acid or Thr (Bzl), Ser (Bzl) or NR8C (QR10)HCO;

R6 = N-protecting group, acetyl, Co-alkyl(1-4C), natural amino acid, lower alkyl, H or R1;

A-B, X-Y = CONH, CH2NH, COCH2, CH2CH2, CH2S, CH2O, CO-N (lower alkyl), CH2-N(lower alkyl) or PHO2-NH;

Any available H on any carbon or nitrogen in (I)-(VI) and any of the corresponding substituents may be in part or totally substituted by halo, alkyl, aryl, OH, CO-lowere alkyl, O-lower alkyl, O-CH2-aryl, O-aryl, or cyclopropyl, cyclopentyl, cyclohexyl, a 5 or 6-membered aromatic or aliphatic N-heterocycle which:

(a) contains N, O and/or S, and

(b) is optionall benzofused or optionally substituted on one or more other C-atoms by lower alkyl, aryl and/or oxo.

ACTIVITY - Osteopathic; Antirheumatic; Antiarthritic; Cytostatic; Neuroprotective; Antiinflammatory; Nootropic; Gastrointestinal-Gen.; Cerebroprotective; Hemostatic; Vulnerary; Ophthalmological;

Searched by: Mary Hale 571-272-2507 REM 1D86

Immunosuppressive; Respiratory-Gen.; Antilipemic; Gynecological.

MECHANISM OF ACTION - Matrix-Metalloproteinase-Inhibitor. Compound (A) exhibited Ki values of 5 x 10-9 M for MMP-9 and 1.9 x 16-6 for dmMMP-8, respectively.

USE - The compounds are matrix metalloproteinase inhibitors useful for **treating** degenerative joint diseases, rheumatoid arthritis, osteoarthritis, cancer, metastasis, tumor invasion, multiple sclerosis, paradontosis, fibrosis, Alzheimer's disease, inflammatory bowel disease, **neurodegenerative** diseases, cerebral hemorrhage, wound healing, degenerative eye disease, aneurysm, artificial joint replacement, organ transplantation, emphysema, cholesteatoma and pre-eclampsia (claimed).

ADVANTAGE - The peptide nature of the inhibitors makes them similar to natural substances. However, in spite of the peptide character of the inhibitors, the P1-P1 peptide bond shows a high resistance to cleavage by proteinases.

Dwg.0/1

L54 ANSWER 19 OF 26 EMBASE on STN

2000368921 EMBASE The molecular genetic basis of the neuronal ceroid lipofuscinoses. Gardiner R.M.. R.M. Gardiner, Department of Pediatrics, Royal Free/Univ. Coll. Medical Sch., University College London, 5 University Street, London WC1E 6JJ, United Kingdom. Neurological Sciences 21/3 SUPPL. (S15-S19) 2000.

Refs: 36.

ISSN: 1590-1874. CODEN: NESCCX. Pub. Country: Italy. Language: English. Summary Language: English.

AB The neuronal ceroid lipofuscinoses (NCLs) are a group of inherited **neurodegenerative** disorders characterized by the presence of autofluorescent lipopigment in neurons and other cell types. The childhood onset types display autosomal recessive inheritance. Naturally occurring animal NCLs have been described in many species including mouse, sheep and dog. In the last decade major advances have occurred in the molecular genetic analysis of the NCLs. Six disease gene loci have been mapped, and five disease genes have been isolated. Two of these encode lysosomal enzymes: CLN1 encodes palmitoyl-protein thioesterase (PPT), and CLN2 encodes tripeptidyl peptidase 1 (TPP1). The remaining three, CLN3, CLN5 and CLN8 encode putative membrane proteins of unknown function. The murine orthologue of CLN8 causes motor neuron degeneration (mnd), a mouse model of NCL. These advances have revolutionized diagnosis and classification, but a unified theory of pathogenesis and effective **treatment** remain elusive.

L54 ANSWER 20 OF 26 HCAPLUS

2001:678460 Document No. 136:230140 Apoptosis and **neurodegeneration** : the role of caspases. Nicotera, P. (Faculty of Biology, University of Konstanz, Konstanz, D-78457, Germany). Pharmacology of Cerebral Ischemia, [International Symposium on the Pharmacology of Cerebral Ischemia], 8th, Marburg, Germany, July 23-26, 2000, 3-9. Editor(s): Krieglstein, Josef; Klumpp, Susanne. Medpharm Scientific Publishers: Stuttgart, Germany. (English) 2000. CODEN: 69BUXN.

AB A review. The execution of the apoptotic program involves a relatively limited number of pathways that converge on the activation of the caspase family of proteases. However, there is increasing evidence that apoptotic-like features can be found also when cells are **treated** with inhibitors of caspases such as the cell permeable **tripeptide** , Z-Val-Ala-Asp-fluoromethyl-ketone (Z-VAD-fmk), or similar compds. This has posed the question as to whether death with apoptotic features can still occur in a caspase independent way, and whether caspase inhibitors may then be used to **treat** diseases characterized by excessive apoptosis. In several **neurodegenerative** diseases metabolic defects are often linked to the loss of neuronal connectivity and cell

loss. The resulting ATP depletion can preclude caspase activation, and consequently switch execution of cell death towards necrosis. A block or partial inhibition of the typical apoptotic demise may have profound implications in vivo, as persistence within the nervous system of damaged, but "undead" cells, followed by delayed lysis may favor neuroinflammatory reactions. Furthermore, caspases may be involved in loss of neurons, but not in the loss of connectivity that seems to initiate degenerative processes in the nervous system. Some recent findings, which suggest that degenerating neurons may use multiple execution pathways will be discussed.

L54 ANSWER 21 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN
1999:674586 Document No. 131:309037 Execution of apoptosis. Converging or diverging pathways?. Nicotera, Pierluigi; Leist, Marcel; Single, Barbara; Volbracht, Christiane (Faculty Biology, Univ. Konstanz, Konstanz, D-78457, Germany). Biological Chemistry, 380(9), 1035-1040 (English) 1999. CODEN: BICHF3. ISSN: 1431-6730. Publisher: Walter de Gruyter GmbH & Co. KG.
AB A review is given with many refs. on diverging execution pathways used by cells, with different implications in pathol. and **therapy**. There is increasing evidence that apoptosis and necrosis represent only 2 of several possible ways for cells to die. These 2 types of demise can occur simultaneously in tissues or cell cultures exposed to the same stimulus, and often local metabolic conditions and the intensity of the same initial insult decide the prevalence of either apoptosis or necrosis. Recent work has shown that execution of the apoptotic program involves a relatively limited number of pathways. According to a general view, these would converge to activate the caspase family of proteases. However, there is increasing evidence that apoptotic-like features can be observed also in cells where caspases are inhibited by cell-permeable **tripeptides**, such as z-VaD-Ala-Asp-fluoromethyl ketone (z-VAD-fmk), or analogous compds. This has posed the question as to whether apoptosis mayor may not occur in a caspase independent way, and whether caspase inhibitors may be effective in the **treatment** of disease. Also relevant is the understanding that low intracellular energy levels during apoptosis can preclude caspase activation, and consequently decide the occurrence and mode of demise in damaged cells. In vivo, incomplete execution of damaged cells by apoptosis may have profound implications, as their persistence within a tissue, followed by delayed lysis, may elicit delayed pro-inflammatory reactions.

L54 ANSWER 22 OF 26 MEDLINE on STN DUPLICATE 8
1999101174. PubMed ID: 9886083. Peroxynitrite-induced alterations in synaptosomal membrane proteins: insight into oxidative stress in Alzheimer's disease. Koppal T; Drake J; Yatin S; Jordan B; Varadarajan S; Bettenhausen L; Butterfield D A. (Department of Chemistry, Center of Membrane Sciences, University of Kentucky, Lexington 40506-0055, USA.) Journal of neurochemistry, (1999 Jan) 72 (1) 310-7. Journal code: 2985190R. ISSN: 0022-3042. Pub. country: United States. Language: English.
AB Peroxynitrite (ONOO) is a highly reactive, oxidizing anion with a half-life of <1 s that is formed by reaction of superoxide radical anion with nitric oxide. Several reports of ONOO--induced oxidation of lipids, proteins, DNA, sulfhydryls, and inactivation of key enzymes have appeared. ONOO- has also been implicated as playing a role in the pathology of several **neurodegenerative** disorders, such as Alzheimer's disease (AD) and amyotrophic lateral sclerosis, among others. Continuing our laboratory's interest in free radical oxidative stress in brain cells in AD, the present study was designed to investigate the damage to brain neocortical synaptosomal membrane proteins and the oxidation-sensitive enzyme glutamine synthetase (GS) caused by exposure to ONOO-. These synaptosomal proteins and GS have previously been shown by us and others to have been oxidatively damaged in AD brain and also following **treatment** of synaptosomes with amyloid beta-peptide. The results

of the current study showed that exposure to physiological levels of ONOO- induced significant protein conformational changes, demonstrated using electron paramagnetic resonance in conjunction with a protein-specific spin label, and caused oxidation of proteins, measured by the increase in protein carbonyls. ONOO- also caused inactivation of GS and led to neuronal cell death examined in a hippocampal cell culture system. All these detrimental effects of ONOO- were successfully attenuated by the thiol-containing antioxidant **tripeptide** glutathione. This research shows that ONOO- can oxidatively modify both membranous and cytosolic proteins, affecting both their physical and chemical nature. These findings are discussed with reference to the potential involvement of ONOO- in AD **neurodegeneration.**

L54 ANSWER 23 OF 26 HCAPLUS COPYRIGHT 2004 ACS on STN
1999:581970 Document No. 131:318018 α-MSH Peptides Inhibit Production of Nitric Oxide and Tumor Necrosis Factor-α by Microglial Cells Activated with β-Amyloid and Interferon γ. Galimberti, Daniela; Baron, Pierluigi; Meda, Lucia; Prat, Elisabetta; Scarpini, Elio; Delgado, Rene; Catania, Anna; Lipton, James M.; Scarlato, Guglielmo (Institute of Neurology, Dino Ferrari Center, IRCCS Ospedale Maggiore Policlinico, University of Milan, Milan, 20122, Italy). Biochemical and Biophysical Research Communications, 263(1), 251-256 (English) 1999. CODEN: BBRCA9. ISSN: 0006-291X. Publisher: Academic Press.

AB α-MSH is an ancient tridecapeptide with potent inhibitory activity in all major forms of inflammation. The anti-inflammatory message sequence of α-MSH resides in the C-terminal **tripeptide** α-MSH[11-13]. The authors tested the influence of α-MSH[1-13] and of α-MSH[11-13] in a cultured murine microglia cell line known to produce nitric oxide (NO-2) and tumor necrosis factor (TNFα) when stimulated with β-amyloid protein (Aβ). Melanocortin peptides significantly inhibited release of both NO-2 and TNFα into cell-free supernatants from microglia stimulated with Aβ[1-42] or Aβ[25-35] peptides and interferon γ (IFNγ). Northern blot anal. demonstrated that α-MSH[1-13] and α-MSH[11-13] inhibited accumulation of inducible nitric oxide synthase (iNOS) and TNFα mRNA was triggered by Aβ stimulation. Aβ/microglial interaction is believed to promote the progression of inflammatory and **neurodegenerative** changes in senile plaques in Alzheimer's disease. The authors' data indicate that α-MSH peptides might be used to modulate the local response of the brain to Aβ deposition in this **neurodegenerative** disease. (c) 1999 Academic Press.

L54 ANSWER 24 OF 26 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
AN 1998-239848 [21] WPIDS
AB WO 9814202 A UPAB: 19980528
Patient with, or susceptible to, a condition requiring an increase in one of the neural enzymes choline acetyltransferase (ChAT), nitric oxide synthase (NOS) or glutamic acid decarboxylase (GAD) is **treated** by increasing the effective amount of the **tripeptide** GPE (I), or its analogues, in the central nervous system (CNS).

USE - Increasing GPE levels up-regulates expression of the specified enzymes and is useful for **treatment** or prevention of motor neuron or Alzheimer's diseases, muscular dystrophy, peripheral or autonomic neuropathy, memory loss and age-related **neurodegeneration** (requiring ChAT); post-asphyxial seizures, convulsions, **neurodegenerative** disease or hypoxic/ischaemic brain injury (GAD), or subarachnoid haemorrhage, transient ischaemic attacks, stroke, multi-infarct dementia, cerebral vasculitis and traumatic brain injury (NOS).

GPE is already known as a neuro-protectant (preventing or reducing neural cell death).

GPE or its analogues and prodrugs can be administered peripherally,

e.g. parenterally, orally or rectally, but particularly GPE is delivered directly to the CNS, e.g. by lateral cerebro-ventricular injection or by surgical insertion of a shunt in the brain.

A preferred dose is 0.4-10000 mu g/kg for central delivery.

Dwg.1/6

L54 ANSWER 25 OF 26 MEDLINE on STN DUPLICATE 9

97042765. PubMed ID: 8887964. Selective role of glutathione in protecting human neuronal cells from dopamine-induced apoptosis. Gabby M; Tauber M; Porat S; Simantov R. (Department of Molecular Genetics, Weizmann Institute of Science, Rehovot, Israel.) Neuropharmacology, (1996 May) 35 (5) 571-8. Journal code: 0236217. ISSN: 0028-3908. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The role of glutathione and other antioxidants in dopamine-induced apoptosis has been analyzed in cultures of the human neuronal cell line NMB. Apoptosis, induced by 0.1-0.3 mM dopamine, was blocked by glutathione in a dose- and time-dependent manner. This was observed by monitoring cell morphology, cell viability, and the release of the cytosolic enzyme lactate dehydrogenase into the culture medium. L-Cysteine and N-acetylcysteine had a similar effect in protecting against dopamine neurotoxicity, but at lower concentrations than glutathione. The dopamine-induced alteration in the cell cycle profile, detected by flow cytometry (FACS), and intranucleosomal DNA fragmentation, were both blocked by glutathione. **Treatment** of NMB cells with buthionine sulfoximine, an irreversible inhibitor of gamma-glutamylcysteine synthetase, increased the neurotoxic effect of, dopamine, suggesting that endogenous glutathione participates in reducing dopamine neurotoxicity. The relationship between glutathione and dopamine was further investigated by testing the effect of dopamine on the endogenous glutathione level. Dopamine decreased glutathione levels within 16-24 hr; however, this effect was preceded by a transient increase in the level of the **tripeptide** within the first 0.5-7 hr. Two other types of endogenous antioxidants, (+)-alpha-tocopherol (vitamin E) and ascorbic acid (vitamin C), were tested; vitamin E (at 1-100 microgram/ml) was inactive against dopamine toxicity, whereas vitamin C had no effect at 0.05-0.2 mM, but increased dopamine toxicity at 0.5-2 mM. The results indicate that glutathione has a selective role in protecting human neural cells from the toxic effect of dopamine. This study may contribute, therefore, to a better understanding of the mechanisms underling the excessive loss of dopaminergic neurons in **neurodegenerative** diseases, such as Parkinsonism, and in the aging process.

L54 ANSWER 26 OF 26 MEDLINE on STN DUPLICATE 10

94046987. PubMed ID: 8230139. Peptide alpha-keto ester, alpha-keto amide, and alpha-keto acid inhibitors of calpains and other cysteine proteases. Li Z; Patil G S; Golubski Z E; Hori H; Tehrani K; Foreman J E; Eveleth D D; Bartus R T; Powers J C. (School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta 30332-0400.) Journal of medicinal chemistry, (1993 Oct 29) 36 (22) 3472-80. Journal code: 9716531. ISSN: 0022-2623. Pub. country: United States. Language: English.

AB A series of dipeptidyl and tripeptidyl alpha-keto esters, alpha-keto amides, and alpha-keto acids having leucine in the P2 position were synthesized and evaluated as inhibitors for the cysteine proteases calpain I, calpain II, cathepsin B, and papain. In general, peptidyl alpha-keto acids were more inhibitory toward calpain I and II than alpha-keto amides, which in turn were more effective than alpha-keto esters. In the series Z-Leu-AA-COOEt, the inhibitory potency decreased in the order: Met (lowest KI) > Nva > Phe > 4-Cl-Phe > Abu > Nle (highest KI) with calpain I, while almost the reverse order was observed for calpain II. Extending the dipeptide alpha-keto ester to a **tripeptide** alpha-keto ester yielded significant enhancement in the inhibitory potency toward cathepsin B, but smaller changes toward the calpains. Changing the ester group in

the alpha-keto esters did not substantially decrease KI values for calpain I and calpain II. N-Monosubstituted alpha-keto amides were better inhibitors than the corresponding alpha-keto esters. alpha-Keto amides with hydrophobic alkyl groups or alkyl groups with an attached phenyl group had the lower KI values. N,N-Disubstituted alpha-keto amides were much less potent inhibitors than the corresponding N-monosubstituted peptide alpha-keto amides. The peptide alpha-keto acid Z-Leu-Phe-COOH was the best inhibitor for calpain I (KI = 0.0085 microM) and calpain II (KI = 0.0057 microM) discovered in this study. It is likely that the inhibitors are transition-state analogs and form tetrahedral adducts with the active site cysteine of cysteine proteases and form hydrogen bonds with the active site histidine and possibly another hydrogen bond donor in the case of monosubstituted amides. Several inhibitors prevented spectrin degradation in a platelet membrane permeability assay and may be useful for the **treatment** of diseases which involve **neurodegeneration.**